Development and Psychometric Evaluation of a Health-Related Quality of Life Questionnaire for Children and Adolescents with Intoxication-Type Inborn Errors of Metabolism

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Abstract

Intoxication-type inborn errors of metabolism (IT-IEM) are a group of rare genetic diseases that include urea cycle disorders and organic acidurias. Affected patients depend on a strict nutritional diet and are at risk of severe metabolic crises. Impact of the disease on everyday life remains crucial and can be measured by health-related quality of life (HrQoL). This dissertation project sought to develop and psychometrically evaluate the first disease-specific HrQoL questionnaire for paediatric IT-IEM patients.

A systematic literature review laid the foundation of the project, summarizing previous research on HrQoL in IT-IEM patients. With the goal of identifying core topics relating to HrQoL in the affected population, patients and parents were then invited to focus group interviews. Systematic content analysis allowed to identify 14 categories within the three primary dimensions of physical, mental, and social HrQoL. Based on these categories, a set of questions — both for self-rating (patients) and proxy-rating (parent) — were constructed for patients from 4 to 7 years (2 to 7 for proxy rating) and from 8 to 18 years. This thesis psychometrically evaluated the versions for patients from 8 to 18 years.

Carefully developed in accordance with established guidelines, the new questionnaire MetabQoL 1.0 appears to be a promising step towards measuring the subjective impact of IT-IEM among patients, both in research and clinical practice.

Zusammenfassung

Stoffwechselkrankheiten vom Vergiftungstyp (Englisch: IT-IEM) sind eine Gruppe seltener, angeborener Krankheiten wie Harnstoffzyklusstörungen und Organoazidurien. Patienten sind auf eine strikte Diät angewiesen und leben mit dem Risiko schwerwiegender Stoffwechselkrisen. Die Krankheit belastet den Alltag der Patienten, was mit dem Konstrukt der gesundheitsbezogenen Lebensqualität (Englisch: HrQoL) gemessen werden kann. Dieses Dissertationsprojekt hatte zum Ziel den ersten krankheitsspezifischen Fragebogen zu HrQoL bei IT-IEM Patienten zu entwickeln und psychometrisch zu evaluieren.

Zu Beginn wurde in einer systematischen Übersichtsarbeit bisherige Forschung zu HrQoL bei IT-IEM analysiert. Um zentrale Themen bezüglich HrQoL für Betroffene zu identifizieren, wurden Patienten und Eltern zu Fokusgruppeninterviews eingeladen. Mithilfe systematischer Inhaltsanalyse der Interviews, wurden 14 Kategorien in den drei Hauptdimensionen der physischen, mentalen und der sozialen HrQoL benannt. Darauf basierend wurden Fragen zur HrQoL entwickelt, jeweils für Patienten im Alter von 4 bis 7 Jahren (2 bis 7 bei Fremdauskunft) und 8 bis 18 Jahren. Alle Fragen wurden sowohl für Selbstauskunft (Patient) als auch für Fremdauskunft (Eltern) bereitgestellt.

Sorgfältig und anhand etablierter Richtlinien entwickelt, ist der neue Fragebogen MetabQoL 1.0 ein vielversprechender Schritt zur Erfassung der subjektiven Belastung von IT-IEM auf Patienten in Forschung und klinischer Praxis.

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Abbreviations

BASC	Behavior Assessment System for Children
CBCL	Child Behavior Checklist
CNS	Central nervous system
DISABKIDS	Instrument to assess health-related quality of life in children with chronic conditions
HrQoL	Health-related quality of life
IEM	Inborn errors of metabolism
IT-IEM	Intoxication-type inborn errors of metabolism
MetabQoL 1.0	Health-related quality of life questionnaire for paediatric patients with intoxication-type inborn errors of metabolism (*Metab* = Metabolic, *QoL* = quality of life)
MSUD	Maple syrup urine disease
OA	Organic acidurias
PedsQL	Pediatric Quality of Life Inventory
QoL	Quality of Life
UCD	Urea cycle disorders
TYR 1	Tyrosinemia type 1

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A. General Introduction

1. Intoxication-type inborn errors of metabolism

Intoxication-type inborn errors of metabolism (IT-IEM) are a group of rare metabolic diseases that include urea cycle disorders (UCD), organic acidurias (OA), maple syrup urine disease (MSUD) and tyrosinemia type 1 (TYR 1). Incidence rates are currently estimated to be approximately 1:35'000 for UCD (Marshall L Summar et al., 2013), 1:21'000 for OA (Dionisi-Vici et al., 2002), 1:185'000 for MSUD (Chuang & Shih, 2001), and 1:100'000 for TYR 1 (De Laet et al., 2013), but all of these are probably underestimates, due to the under-diagnosis of fatal or atypical cases (Häberle et al., 2012).

Most IT-IEM are transmitted genetically following an autosomal-recessive inheritance pattern (Nassogne, Héron, Touati, Rabier, & Saudubray, 2005). The autosomal recessive pattern generally implies that both of a patient's parents are genetic carriers of the disease, but completely healthy because they have one intact gene. In this case, there is a 25% risk for each pregnancy that a child of these parents will be affected. Due to this inheritance pattern, IT-IEM are more prevalent in families with a history of consanguinity. Furthermore, the incidence may be specifically high in certain populations due to founder effects. This is the case for MSUD in the Old Order Mennonite community, in which it has an estimated incidence of approximately 1:150 (Love-Gregory, Dyer, Grasela, Hillman, & Phillips, 2001).

As an exception, the most common UCD, OTC-deficiency (see Figure 2), is transmitted via an X-linked recessive inheritance pattern (Nassogne et al., 2005). Females carrying the diseases on one of their two X chromosomes may have any degree of disease severity, depending on skewed X-inactivation. Many females are mildly affected and may exhibit atypical symptoms, so that the diagnosis may be missed. Males, who by definition only carry the one affected X chromosome, generally are more severely affected and present with symptoms earlier in life.

Biochemically, the genetic defect results in the malfunction or dysfunction of a given enzyme (or, in one instance, a transport protein). Enzymes serve as biological catalysts and ease the transformation of one substance into another. If the enzyme is dysfunctional, the substrates cannot be metabolized properly and accumulate, while the product remains either missing or diminished for use in later metabolic steps. Metabolic pathways with functional versus dysfunctional enzymes are schematically depicted in Figure 1, including the resulting problems with dysfunctional enzymes and corresponding therapeutic approaches. In UCD, there is a perturbance in the metabolism of ammonia, a product of protein catabolism. Other IT-IEM involve other pathways of amino acid catabolism. Amino acids are the building blocks of protein. An overview of metabolic pathways relevant for each IT-IEM, including the site of the defect, is depicted in Figures 3 and 4 (Ruzkova et al., 2015; Zschocke & Hoffmann, 2012).

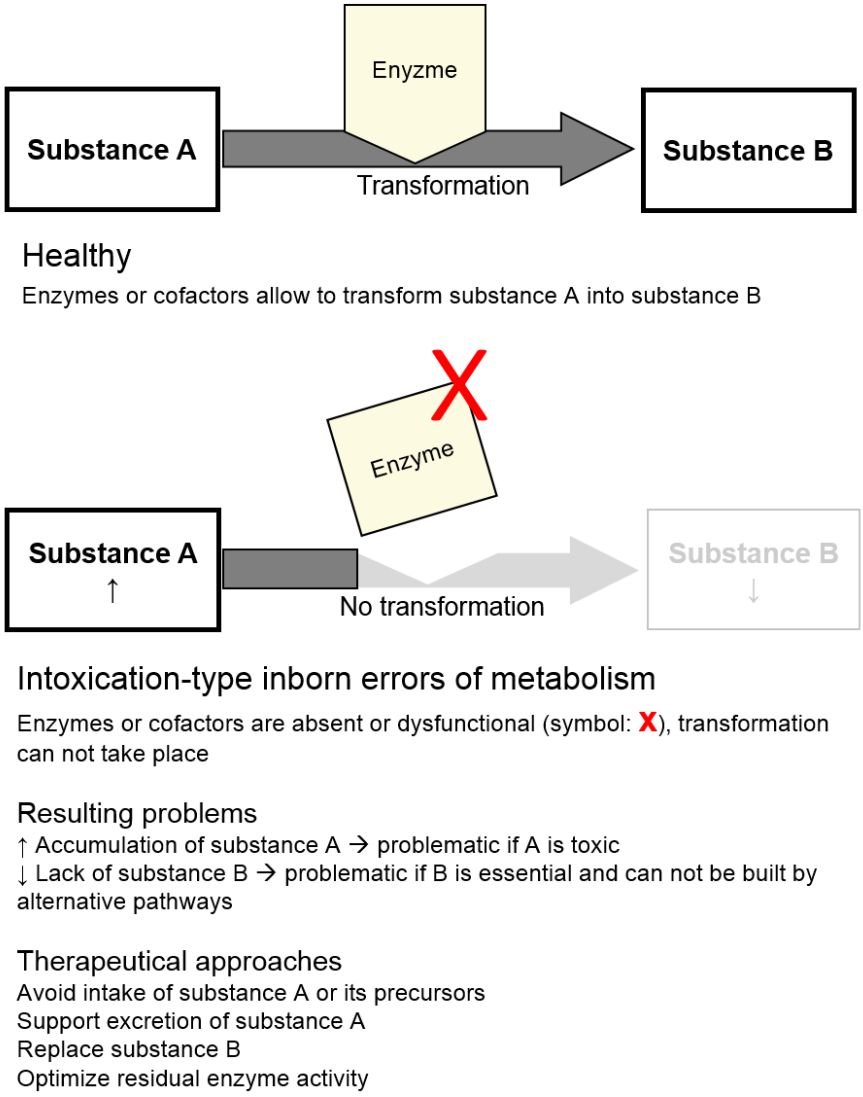

Figure 1: Basic function of enzymes in healthy persons versus IT-IEM patients

In patients with complete enzyme deficiencies, symptoms typically present in the neonatal period, characterized by acute deterioration in the infant's clinical condition. One major problem is the accumulation of toxic substances that cannot be metabolized properly (Figure 1: Substance A), such as ammonia in UCD. This so-called metabolic crisis may lead to coma, death or severe sequelae if left untreated (Baumgartner et al., 2014; Häberle et al., 2012). In patients with partial enzyme deficiencies, the disease may become manifest at any age and include a wide range of less-specific symptoms like neurodevelopmental delay, failure to thrive, or psychiatric symptoms like hallucinations or personality change (Baumgartner et al., 2014; Häberle et al., 2012). Metabolic crises can occur in all patients at any age, often triggered by febrile infections, vomiting, fasting, excessive protein load, psychological stress, or intense physical excersise (Häberle et al., 2012). Crises often cause brain damage in survivors, resulting in neurological symptoms like movement or

developmental deficits. In the long term, some IT-IEM can have specific organ sequelae; for example, kidney disease or cardiomyopathy in some OA (Baumgartner et al., 2014).

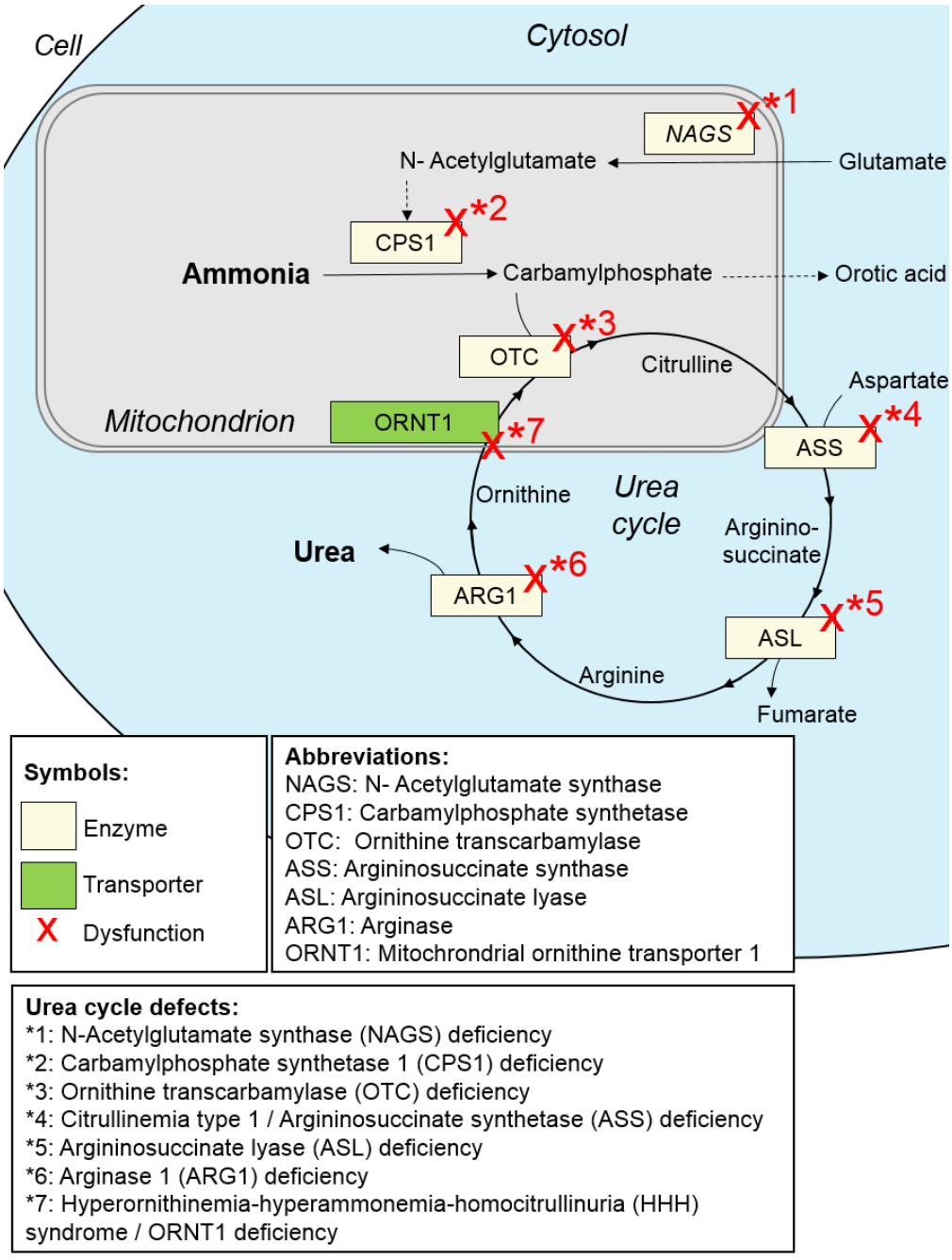

Figure 2: Biochemical localisation of urea cycle disorders in the urea cycle pathway

The urea cycle transforms the toxic substance ammonia into urea. All urea cycle disorders result in the accumulation of ammonia. As an exception, HHH syndrome / ORNT1 deficiency is not manifest as an enzyme defect, but as a transporter defect. The content of this figure was adapted and simplified from Zschocke and Hoffmann (2012).

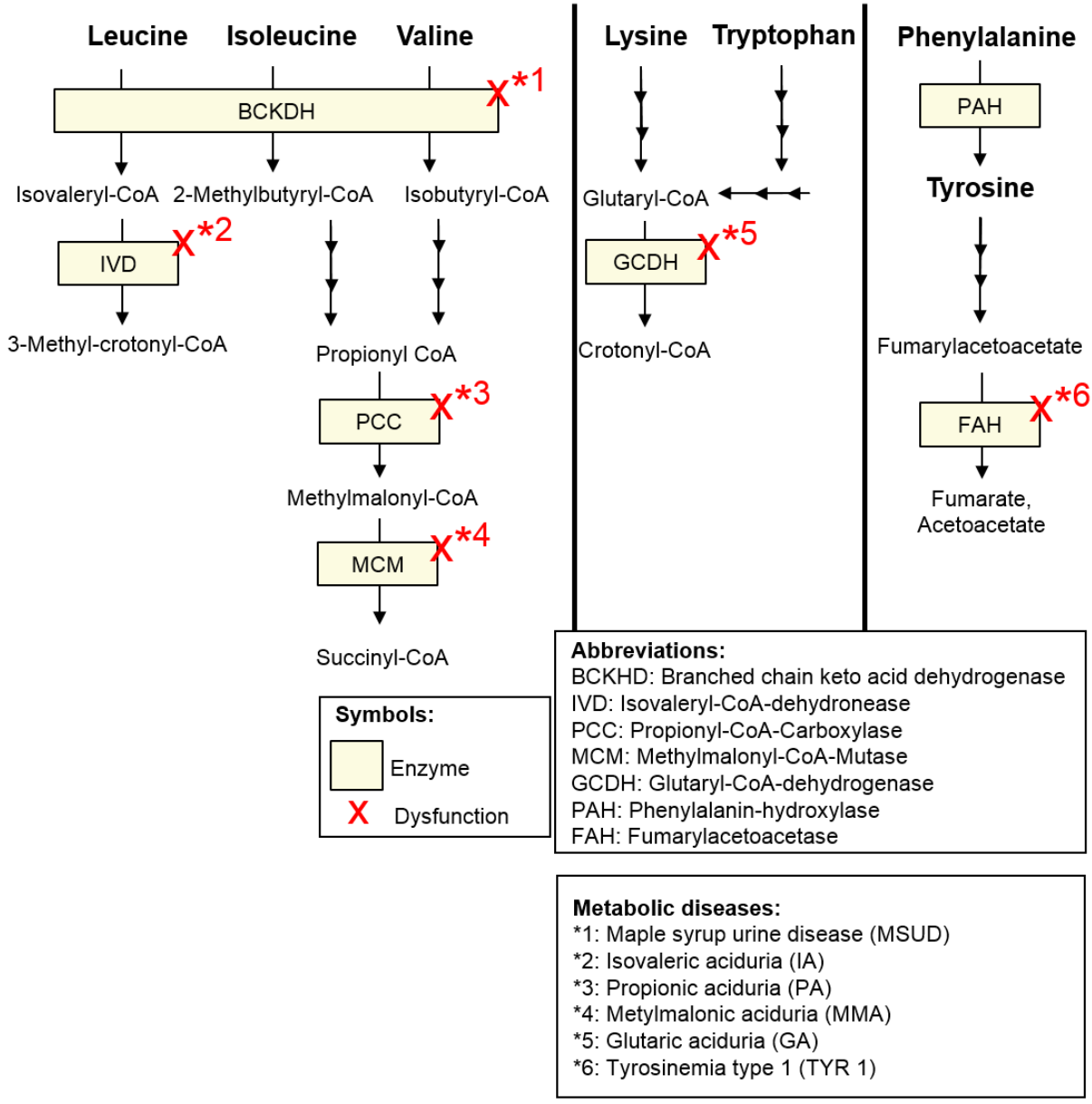

Figure 3: Biochemical localisation of organic acidurias, maple syrup urine disease, and tyrosinemia type 1 in different metabolic pathways

These diseases all affect amino acid (leucine, isoleucine, valine, lysine, tryptophan, phenylalanine) degradation. The content of this figure was adapted and simplified from Ruzkova (2015) and Zschocke and Hoffmann (2012).

Due to their sometimes non-specific presentation and rarity, IT-IEM are often not recognized early enough to prevent death or severe brain damage, even if relatively effective therapies are available (Baumgartner et al., 2014). For some diseases, the pathophysiological mechanisms are incompletely understood and current treatment practice may be insufficient to prevent severe impairment. Thus, outcomes remain poor for many IT-IEM .

Short-term (emergent) and long-term treatment must be distinguished. Short-term treatment aims to stabilize an acutely ill patient by, for example, having them cease all protein intake and start specific drug treatment and potentially undergo extracoporeal detoxification by

means of dialysis (Baumgartner et al., 2014). Long-term treatment generally includes a low-protein diet, since some protein or specific amino acid cannot be metabolized properly. This being said, protein in general and essential amino acids in particular are required for growth and development. Therefore, patients must be supplied with synthetic amino acid mixtures in the form of drinks or powders. These mixtures need to be taken daily, ideally divided into 2-3 doses in order to provide sufficient total protein. Additionally, medication can be prescribed to increase the excretion of toxic substances (Häberle et al., 2012). Feeding problems are common in patients with IT-IEM, which is why tube feeding may be necessary in certain cases (Baumgartner et al., 2014). Usually, this entails a gastric feeding tube, which allows to administer medication and nutritional supplements to maintain satisfactory nutritional status and metabolic stability (Baumgartner et al., 2014). In selected patients with a UCD, liver transplantation can be an option (Leonard & McKiernan, 2004). Treatments like gene therapy, enzyme replacement, and liver cell transplantation are currently at different stages of development, but not yet routinely offered to IT-IEM patients (Baumgartner et al., 2014; Häberle et al., 2012).

2. Health-related quality of life

2.1. Definition

The term Quality of Life (QoL) was first used in social sciences in the seventies (Bullinger, 2014). At this time, medicine was evolving rapidly in many industrial countries, resulting in major improvements in both diagnostics and treatment. This led to an increase in the number of patients surviving with a wide range of chronic diseases (Landolt & Sennhauser, 2007). Consequently, survival ceased to be the only indicator of a positive treatment outcome, so that a broader concept of health, described by the World Health Organisation (WHO) in 1948, gained importance. The WHO defined health as a state of complete physical, mental and social well-being, as opposed to being merely the absence of disease (World Health Organisation, 1948).

Today, the WHO definition for health is often cited as the basis of research on health-related quality of life (HrQoL). HrQoL must be distinguished from the broader term QoL, which not only encapsulates health-related themes, but also issues like political freedom and material security (Bullinger, 2009). Of the many existing definitions of HrQoL, most agree that HrQoL is subjective and multidimensional. There is consensus that physical, mental, and social functioning are its three core dimensions (Landolt & Sennhauser, 2007; Rajmil et al., 2004). Focusing on young people with chronic illness, the dynamic character of HrQoL, which changes over time, is important to note (Taylor, Gibson, & Franck, 2008). As such, HrQoL of a child with a chronic condition could decline because the underlying medical condition worsens, but also because the patient's circumstances change (e.g., transition to a new school adding novel challenges), or because of the patient's self-evaluation of the situation (e.g., adolescents comparing themselves to peers). Equally, such mechanisms might augment HrQoL. Throughout this present thesis, the definition of HrQoL proposed by Varni, Seid, and Rode (1999) will be used, since its focus is on disease and treatment and matches the examined population. HrQoL is thereby explained as "a patient's perception of the impact of disease and treatment on functioning in a variety of dimensions including physical, psychological and social domains" (Varni et al., 1999, p.126). This definition is depicted with examples in Figure 4. Importantly, the term *domain* is often referred to as a *dimension* or *scale* in questionnaire development; as such, these terms are used interchangeably throughout the following sections of this thesis.

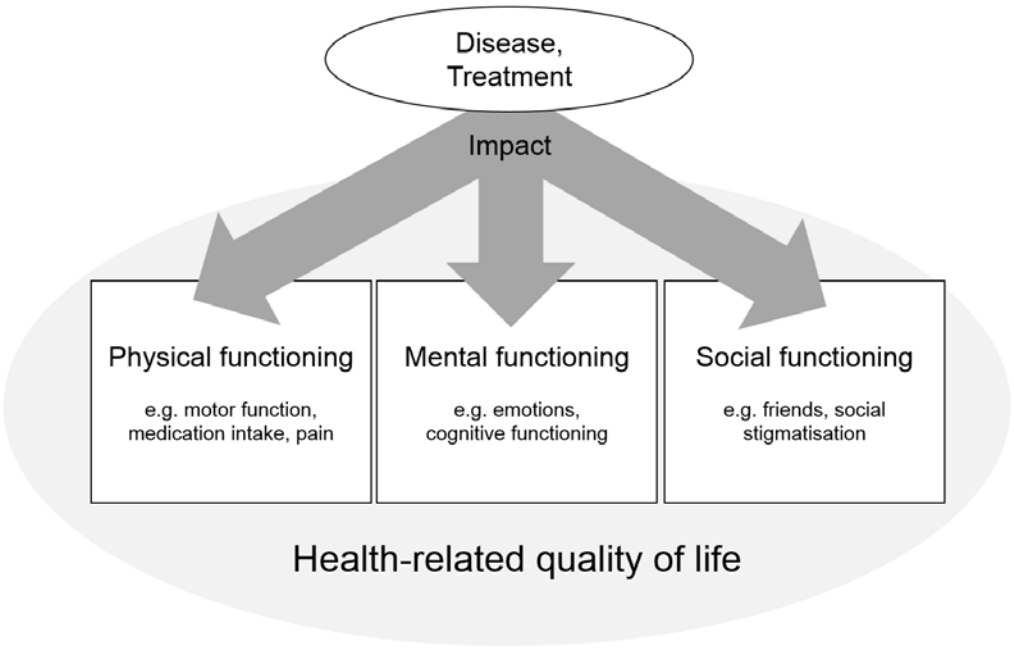

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Figure 4: Health-related quality of life
Based on the definition of Varni et al. (1999)

2.2. Considerations regarding HrQoL measurement

Different considerations must be taken into account when developing, applying, and evaluating HrQoL measurements. Thus, decisions about (1) the informant (patient or proxy), (2) the modality of assessment, (3) the instrument's specificity, and (4) age-related issues need to be made.

Informant: self- versus proxy-assessments

When HrQoL research first started to be conducted in paediatric populations, patients' HrQoL was predominantly rated by medical staff (Landolt & Sennhauser, 2007). However, given that HrQoL is generally deemed a subjective construct, the view emerged that HrQoL might be rated differently and more accurately from a patient perspective.

Since HrQoL is a construct that reflects the subjective view of an individual, self-reporting is the method of choice when choosing the informant (Matza et al., 2013). In some situations (e.g., when patients are very young or cannot answer the questionnaire due to some impairment), supplementation with proxy ratings (by parents or medical staff) is the best alternative. Furthermore, proxy-ratings can be very valuable to use in addition to self-ratings to gain insights from multiple perspectives (Eiser & Jenney, 2007). However, one must be aware that only poor to moderate correlations have been identified between self- and proxy-

assessments, and that good agreement has been shown mostly for more observable facets like physical symptoms. Other measures from the mental dimension, like cognition or emotions, do not correlate well (Eiser & Jenney, 2007). In general, agreement is better in sick than in healthy children (Eiser & Jenney, 2007). Interestingly, sick children usually rate their HrQoL better than their parents do, while proxy-ratings by parents tend to be higher than self-ratings in healthy children (Upton, Lawford, & Eiser, 2008). In summary, a multiple-informant perspective is preferred, whenever possible, since proxy-ratings are a very important additional source of information, but not interchangeable with self-ratings.

Modality

One can assess HrQoL by letting individuals complete a questionnaire by themselves (with paper and a pencil or on an electronic device) or during an interview (Gerharz, Ravens-Sieberer, & Eiser, 2008). Self-completion is a very efficient method; however, it needs to be used cautiously in the paediatric population since written questionnaires lack certain benefits of in-person interviews, like the provision of additional guidance to the respondent, thereby increasing the comprehensibility and feasibility of the questionnaire, both which are essential characteristics of effective psychological testing. As a trade-off, the greater impact of social desirability bias while answering questions, as well as other potential interviewer effects must be taken into account with face-to-face interviews (R. E. Davis, Couper, Janz, Caldwell, & Resnicow, 2010). For example, children may want to be perceived as particularly brave when they report their symptoms or popular when they report on social inclusion or exclusion.

Instrument specificity

Depending on the goal of the assessment, either generic or disease-specific assessment tools must be chosen. Generic instruments like the KIDSCREEN (The KIDSCREEN Group Europe, 2006) and the PedsQL (Varni et al., 1999) questionnaires are designed to assess HrQoL in all populations, both healthy and diseased. One advantage to such instruments is that they allow for HrQoL to be compared between different groups. However, these instruments lack sensitivity for certain disease-specific HrQoL issues, like diet in diabetic patients. Disease-specific instruments like the PKU-QOL (Regnault et al., 2015) fill this gap, having been designed for use with one disease or a few closely-related diseases in mind in an attempt to assess HrQoL specifically in this population. Thus, these instruments have shown high responsiveness to changes of HrQoL (S. Wiebe, Guyatt, Weaver, Matijevic, & Sidwell, 2003). The downside is that these tools are of limited use when employed to compare diseased versus healthy populations, or groups with different clinically dissimilar diseases.

The modular approach elegantly combines the advantages of generic and disease-specific tools. A basic generic questionnaire can thereby be extended by adding disease-specific tools. One example of the modular approach is the DISABKIDS (The DISABKIDS Group Europe, 2006) questionnaire, which uses a *chronic*-generic basic tool for all patients with a chronic disease, but can then be extended by means of short, disease-specific modules.

Age-related issues in the paediatric population

HrQoL research started later in children than in adults, due to various sources of scepticism towards the applicability of any construct as complex as HrQoL in children (De Civita et al., 2005). Over the last several years, however, several new HrQoL measures have emerged for use in children and adolescents (Solans et al., 2008). Still, several reasons remain as to why HrQoL assessment instruments for the paediatric population deserve special attention (Landolt & Sennhauser, 2007).

First, children have a different understanding of health and disease than adults. Their understanding and beliefs might not be congruent with those that adults have, which hampers comparisons (Bullinger, 2014). Second, areas that define their HrQoL might be specific to children's stage of development. The relevance of school and relationships with peers are examples that are especially important within the paediatric population, even varying in importance between childhood and adolescence. This again emphasizes the need to define HrQoL as a dynamic construct (Taylor et al., 2008). Third, the capacity of children to answer long questionnaires, to understand response option scales, and to interpret different time spans may differ from adults. These challenges can be confronted by using questions and response formats suitable for children (e.g., smiley face scales for very young children), and conducting in-person interviews instead of paper-pencil surveys (Landolt & Sennhauser, 2007).

For all these reasons, the age-sensitivity of assessment instruments is most important. At the same time, age spans must not be chosen too narrow, so one can assess HrQoL with the same instrument over time as the person ages (Eiser & Jenney, 2007). Guidelines related to the use of paediatric patient-reported outcomes by Matza et al. (2013) point out that age considerations depend on many factors, like the population of interest and the form of data collection (paper-pencil, in-person interview). They also state that the developmental state of a child might not always match their chronological age. Nevertheless, they propose generally considering four age groups as best practice, based upon current, empirically-derived understanding (Matza et al., 2013):

(1) Younger than 5-years: in these children, there is no evidence of reliable self-reporting, so only proxy-reporting is recommended.

(2) 5-7 years: self-assessment is recommended, but should be interpreted with caution, due to uneven cognitive capacities between children and contradictory findings about reliability in past studies. It is especially important to maintain clear formatting and age-appropriate vocabulary.

(3) 8-11 years: Children in this age group have attained some level of understanding of health concepts, and have a progressively-expanding cognitive ability to understand tasks. They also possess the regulatory ability to avoid distractions (Bevans, Riley, Moon, & Forrest, 2010). Moreover, there is growing evidence that self-reporting is both feasible and reliable. Nonetheless, vigilance is warranted to ensure that such children understand the questions as intended.

(4) 12-18 years: The reliability and feasibility of self-assessments do not differ significantly between adolescents and adults. However, capturing content validity for this age group must be considered as challenging, due to the unique social and emotional challenges that adolescents face.

2.3. Quality of life in patients with IT-IEM

Relative to other chronic diseases, research on psychosocial issues in IT-IEM patients has started relatively late and remains sparse, as reviewed in detail in part B of this thesis (Zeltner, Huemer, Baumgartner, & Landolt, 2014). The first publications are dated 2006 (Simons et al., 2006) reporting on psychological adjustment, and 2007 (Packman et al., 2007) reporting on HrQoL. The delay to begin such research might be associated with the fact that the diagnosis and treatment of IT-IEM only emerged in recent years, so that suddenly there appeared a growing population of long-term survivors (Batshaw, Tuchman, Summar, & Seminara, 2014). Part B of this thesis reviews studies that assessed HrQoL, psychological adjustment, and adaptive functioning in IT-IEM patients up to April 2013 (Zeltner et al., 2014). Additional studies have been published since then. One publication included as many as 152 patients with either a UCD or some form of OA (Jamiolkowski et al., 2016), in which HrQoL was measured using the generic tool PedsQL by either self-report (if patients were able to understand it) or proxy-report. HrQoL was reported to be in the same range as in the reference population. However, behavioural and emotional problems, identified during a standardized psychiatric interview (Esser, 1989), were identified. Another study that employed the PedsQL uncovered impaired HrQoL in patients with methylmalonic aciduria, a disease belonging to the OA group of disorders, relative to healthy children and children with

other chronic conditions, with lowest scores for school and social functioning (Splinter et al., 2015). Thus, results on HrQoL in IT-IEM remain inconsistent, as in previous research (Zeltner et al., 2014).

As described in our review (Zeltner et al., 2014), methodological shortcomings are a considerable limitation of previous research. Specifically, the lack of a validated, disease-specific HrQoL instrument hampers any sensitive assessment of specific problems among IT-IEM patients. This gap was aimed to be filled by this dissertation project. The following chapter will elaborate on the methodological background that must be considered as one seeks to develop and evaluate a HrQoL questionnaire.

3. Psychometric theory

The development of instruments to measure constructs like HrQoL forces one to confront a variety of challenges, which can be addressed statistically via psychometric theory (Raykov & Marcoulides, 2011). One major challenge is that HrQoL is not directly measurable; as such, it must be considered a construct or latent variable. HrQoL can be rendered measurable by defining indicators of the construct, like items (tasks or questions) in a questionnaire, representing behaviours or thoughts. This process of construct operationalisation has no single, valid solution (Raykov & Marcoulides, 2011). At the end of the operationalisation stage, a construct is represented by a sample of associated indicators, which can differ depending upon the investigators involved in the process. Another challenge of psychological assessments relates to the embedding of a construct of interest within the existing theoretical framework. In the case of developing a disease-specific HrQoL assessment tool, generic HrQoL measures and related constructs need to be taken into account and their relationships elaborated statistically; for example, by exploring correlations (Raykov & Marcoulides, 2011). Finally, measurements in social science are subject to error. The approach of classical test theory, upon which most psychological tests are based, addresses this issue and will be discussed below.

Keeping these challenges in mind, one can define psychometric theory as one that "deals with (a) evaluating the degree to which these problems affect behavioural measurement in a given situation and (b) developing methods to overcome or minimize the adverse impact of these and related problems and challenges" (Raykov and Marcoulides 2011, p. 9).

3.1. Classical test theory

Classical test theory has its roots at the beginning of the last century (Spearman, 1904). Subsequently, it was developed further over many years (Raykov & Marcoulides, 2011). It is one of the theories upon which most commonly-used psychometric tests are based (Moosbrugger & Kelava, 2012). Classical test theory relies on several assumptions, its axioms, among which the most important states that a measured score X is composed of a true score T and an error score E (Moosbrugger & Kelava, 2012):

$$X = T + E$$

The X is all that can be measured, while the true score T is what is of interest. Under the assumption of uncorrelated errors, T can be approximated by computing the mean of

multiple measurements (Moosbrugger & Kelava, 2012). Multiple measurements can be obtained by repeatedly exposing the same test subject to the same item. However, this technique creates memory effects that may bias the result. Alternatively, computing the mean of different items all referring to the same latent variable can allow one to approximate a true score *T* as well (Moosbrugger & Kelava, 2012). With respect to HrQoL, *T* could thereby be estimated using a questionnaire composed of several different items all acting as indicators of HrQoL.

3.2. Quality criteria of psychological tests

Quality criteria are applied to assess the quality of a test, as depicted in Figure 5 (Moosbrugger & Kelava, 2012). They can be classified as either main or auxiliary quality criteria.

Objectivity is the first main quality criteria, addressing the comparability of test results. A test must therefore be objectively related to its implementation, its evaluation, and its interpretation (Moosbrugger & Kelava, 2012). Standardised assessment procedures, the training of individuals to assess and evaluate tests, and detailed manuals all may help to ensure objectivity (Bühner, 2011). To rate the evaluation's objectivity, two evaluators could be given the same test material to work on, after which the results of their evaluation could be compared.

Reliability, as the second main quality criteria, refers to the exactness of a measurement (Moosbrugger & Kelava, 2012). It is strongly associated with the assumptions of classical test theory (Raykov & Marcoulides, 2011), providing information about variance in the observed score (Bühner, 2011). Basically, reliability can be measured by comparing different measurements and examining their inter-correlations. Different measurements are thereby obtained by repeating a test or by dividing a single test into different parts. Reliability has four main components (Moosbrugger & Kelava, 2012). Test-retest reliability is a measure of how strongly correlated scores for the same test are, when administered twice to the same participant within a set time interval. Importantly, this measurement is only meaningful if the construct measured is expected to be relatively stable over time, which would be the case for constructs like intellectual performance (intelligence) and personality traits (Bühner, 2011). Relevance of test-retest reliability during HrQoL assessments is more debatable, since HrQoL is, by definition, a dynamic construct that is sensitive to change over time (Taylor et al., 2008). Furthermore, other influences like transfer or memory effects must be considered (Moosbrugger & Kelava, 2012), especially if the selected test-retest interval is short.

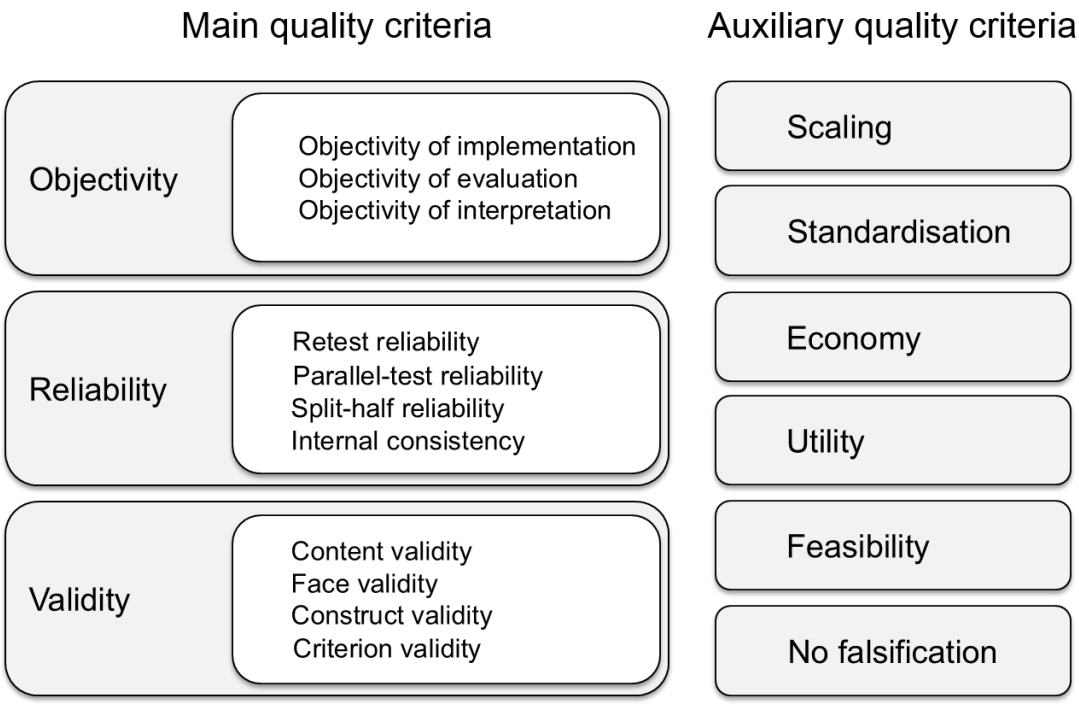


Figure 5: Quality criteria to evaluate psychological tests

A second dimension of reliability is parallel-test reliability, which also requires that two measurements are made on the same subject. It can be computed by correlating the scores of parallel test forms, which consist of very similar items, also referred to as ’item twins’ (Moosbrugger & Kelava, 2012).

Split-half reliability is a very useful way to assess a test’s reliability via one-time administration. Each test item is assigned to one of two subtests, either the A or B half. The two halves are then correlated and the resulting coefficient typically optimised using a formula to consider the original length of the test (Bühner, 2011).

Finally, internal consistency is an expansion of split-half reliability. To measure internal consistency, each item is considered a subtest, and internal consistency is roughly the mean of all their inter-correlations. It is usually assessed by computing Cronbach’s alpha (Bühner, 2011; Cronbach, 1951). Cronbach’s alpha also adjusts the resulting reliability coefficient to consider the original test’s length, as with split-half reliability.

Validity is a third essential quality criteria, which can be defined as the ability of a test to actually measure the construct it was designed to evaluate (Raykov & Marcoulides, 2011). As with reliability, validity has four dimensions. Content validity refers to the extent to which a measure reflects the underlying theoretical construct in a qualitative way. One potential way to evaluate content validity is to ask experts to examine the test to determine how accurately they perceive its items measure the construct of interest (Moosbrugger & Kelava, 2012). However, since multiple definitions often exist for the same construct in the social

sciences, content validity can sometimes be disputed among experts (Raykov & Marcoulides, 2011).

A second component of validity is face validity, which refers to how easily laypersons recognize the construct measured by a test (Moosbrugger & Kelava, 2012).

Construct validity refers to the theoretical foundation of a construct, which can be measured by different means (Moosbrugger & Kelava, 2012). One way is to determine how well the instrument agrees with other measures that quantify the same or a similar construct, a characteristic termed convergent validity. The flip side to this is discriminant validity, which assesses how well the construct of interest is distinctive relative to other constructs. Construct validity also be can evaluated by means of either exploratory or confirmatory factor analytical procedures that seek to detect or verify the construct's dimensionality.

The fourth validity dimension is called criterion validity, which refers to the test's practical use. A test exhibits high criterion validity if its scores are able to predict some behaviour (the criterion) that extends beyond the test; one example of this would be using an intelligence test score as an indicator of school grades.

Besides these main quality criteria, several *auxiliary quality criteria* are needed to thoroughly evaluate a psychological test. A test should have valid instructions for scoring and scaling of items (Bühner, 2011). Furthermore, it should be possible to compare a participant's score against a normative population, which is attained by standardising the test (Bühner, 2011). Additionally, the test's cost, utility and feasibility must be evaluated. One final auxiliary criterion refers to the potential for falsification. It should not be possible for test participants to falsify their test score; for example, for them to somehow fake high intelligence during an intellectual performance test (Bühner, 2011) or feign psychosocial characteristics that they do not have beyond the confines of the test.

All of the afore-mentioned criteria help to describe both the quality of a test and its potential limitations. However, the importance and rating of a single criterion differs, depending on the area of application. As such, reliability in engineering is expected to be much higher than in psychology. This is because psychological constructs can be operationalised differently by different researchers and measurement is much more vulnerable to error, since it can be influenced by factors like the test subject's mood or performance on the test day.

Furthermore, it is important to note that, sometimes, decisions must be made to rate one quality criterion as more important than another. For example, virtually perfect reliability can be achieved by using almost identical test items. An example of this would be using the following three questions — *1. Do your medications bother you? 2. Does taking medication*

bother you? 3. Do you hate taking your medication? — in the same questionnaire. Almost without question, responses to these three items will almost always agree. On the other hand, it is unlikely that these three items adequately address the breadth of the construct of interest (e.g., drug compliance); as such, the content validity of an instrument restricted to these three items would likely be very low (Bühner, 2011).

Another possible trade-off may be between objectivity and feasibility. Especially in paediatric research, it may be necessary to interview test participants in person, rather than let them complete a test by themselves, in order to increase a test's feasibility and verify the participants' understanding of questions. However, doing so may adversely affect the objectivity of the test results, since they might be influenced by characteristics of the different interviewers.

In the field of paediatric HrQoL measurement, the quality of instruments can be evaluated using all of the quality criteria. However, how the different criteria are weighted, in terms of their importance, warrants attention. In children, for example, a test's feasibility is paramount. Additionally, the complexity of the HrQoL construct begs special attention related to validity. Standardisation might be more important in generic HrQoL instruments designed to compare different populations, while disease-specific instruments must be constructed paying utmost attention to content validity, since the content of such a questionnaire will invariably differ from the wide range of generic questionnaires that already are available.

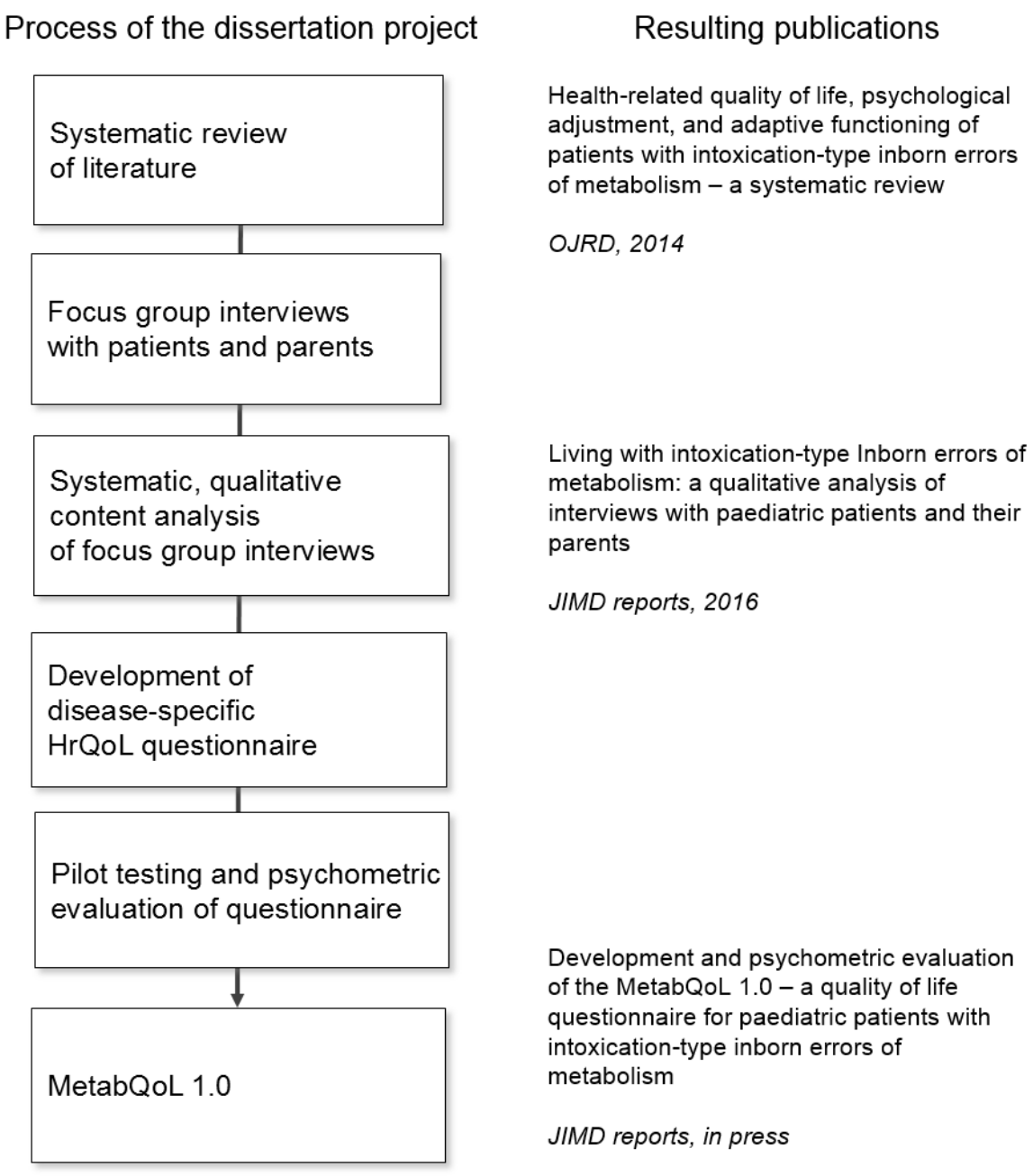
To date, various generic HrQoL questionnaires have been proven to be psychometrically sound (e.g., The KIDSCREEN Group Europe, 2006; Varni et al., 1999; Vogels et al., 1999). Furthermore, many disease-specific instruments have been developed in recent years (Solans et al., 2008). However, a psychometrically-evaluated assessment tool for IT-IEM could not be identified (Zeltner et al., 2014). A targeted assessment of the disease burdens of IT-IEM patients was therefore not yet possible up to now. This gap is, hopefully, filled by this dissertation that aimed to both develop and validate such an instrument. The next chapter will offer an overview of the development process embedded in the dissertation project.

4. Overview of the present dissertation project

This dissertation project was established and funded by the Clinical Research Priority Program radiz – Rare Disease Initiative Zurich. Work was conducted from spring 2013 to autumn 2016. radiz has sought to have researchers of various rare diseases join forces to address a common goal: to "improve the treatment and outcomes of patients with rare diseases" (www.radiz.uzh.ch). Consistent with the radiz mandate, the final goal of this dissertation was to develop a disease-specific questionnaire to assess HrQoL in paediatric IT-IEM patients. The project was characterized by interdisciplinary cooperation between psychologists and physicians at metabolic centres in Dusseldorf, Hamburg, Heidelberg, Innsbruck, and Zurich. This international cooperation was particularly valuable, not only to increase the sample of IT-IEM patients, but also to harness multiple perspectives from investigators at different centres.

Having provided theoretical backgrounds for IT-IEM and HrQoL, and addressed methodological issues pertaining to their study in part A of this thesis, part B consist of three publications, all of which were written during the current project's time-frame. The first of the two publications and, hence, the first of the three chapters is a systematic review that elaborates on the current state of research in the field. The second paper and chapter presents the results of the content analysis of focus group interviews with patients and parents. These results ultimately formed the foundation for questionnaire development. The third chapter, describes the development and psychometric evaluation of the MetabQoL 1.0, the HrQoL instrument for IT-IEM patients that was developed within the confines of the current thesis project. How the publications are organized in the context of the current project is depicted in Figure 6. The dissertation concludes with a part C discussing the questionnaire development process, the quality of the resulting MetabQoL 1.0, potential directions for future research, and the clinical implications of the work presented here.

Figure 6: Flowchart of the present dissertation project with its resulting publications



B. Empirical research

1. Health-related quality of life, psychological adjustment, and adaptive functioning of patients with intoxication-type inborn errors of metabolism – a systematic review

Reference: Zeltner, N. A., Huemer, M., Baumgartner, M. R., Landolt M. A. (2014). Quality of Life, Psychological Adjustment, and Adaptive Functioning of Patients with Intoxication-type Inborn Errors of Metabolism – a Systematic Review. *Orphanet Journal of Rare Diseases, 9*(1): 159. doi: 10.1186/s13023-014-0159-8

1.1. Abstract

Background: In recent decades, considerable progress in diagnosis and treatment of patients with intoxication-type inborn errors of metabolism (IT-IEM) such as urea cycle disorders (UCD), organic acidurias (OA), maple syrup urine disease (MSUD), or tyrosinemia type 1 (TYR 1) has resulted in a growing group of long-term survivors. However, IT-IEM still require intense patient and caregiver effort in terms of strict dietetic and pharmacological treatment, and the threat of metabolic crises is always present. Furthermore, crises can affect the central nervous system (CNS), leading to cognitive, behavioural and psychiatric sequelae. Consequently, the well-being of the patients warrants consideration from both a medical and a psychosocial viewpoint by assessing health-related quality of life (HrQoL), psychological adjustment, and adaptive functioning. To date, an overview of findings on these topics for IT-IEM is lacking. We therefore aimed to systematically review the research on HrQoL, psychological adjustment, and adaptive functioning in patients with IT-IEM.

Methods: Relevant databases were searched with predefined keywords. Study selection was conducted in two steps based on predefined criteria. Two independent reviewers completed the selection and data extraction.

Results: Eleven articles met the inclusion criteria. Studies were of varying methodological quality and used different assessment measures. Findings on HrQoL were inconsistent, with some showing lower and others showing higher or equal HrQoL for IT-IEM patients compared to norms. Findings on psychological adjustment and adaptive functioning were more consistent, showing mostly either no difference or worse adjustment of IT-IEM patients compared to norms. Single medical risk factors for HrQoL, psychological adjustment or adaptive functioning have been addressed, while psychosocial risk factors have not been addressed.

Conclusion: Data on HrQoL, psychological adjustment, and adaptive functioning for IT-IEM are sparse. Studies are inconsistent in their methodological approaches, assessment

instruments and norm populations. A disease-specific standard assessment procedure for HrQoL is not available. Psychosocial risk factors for HrQoL, psychological adjustment, or adaptive functioning have not been investigated. Considering psychosocial variables and their corresponding risk factors for IT-IEM would allow evaluation of outcomes and treatments as well as the planning of effective social and psychological interventions to enhance the patients' HrQoL.

1.2. Introduction

Intoxication-type inborn errors of metabolism (IT-IEM) are a group of inborn errors of metabolism (IEM) which share distinct clinical features. The group encompasses urea cycle disorders (UCD), organic acidurias (OA), tyrosinemia type 1 (TYR 1), and maple syrup urine disease (MSUD). The estimated incidence is about 1:35'000 for UCD (Marshall L Summar et al., 2013), about 1:21,000 for OA (Dionisi-Vici et al., 2002), about 1:100,000 for TYR 1 (De Laet et al., 2013) and about 1:185,000 for MSUD (Chuang & Shih, 2001).

Patients with IT-IEM share two main clinical features: they have to follow a strict diet, and they live with the permanent risk of metabolic crises. These can be triggered by alterations in diet, common infections, or stress but may also occur without predictive circumstances. In cases of metabolic crises, patients immediately require intensified home care or hospitalisation. Despite such efforts, crises remain life-threatening and may cause organ and central nervous system (CNS) damage (Walterfang, Bonnot, Mocellin, & Velakoulis, 2013). To ensure correct diet and an appropriate reaction in risk situations, patients and their families are obliged to develop extensive knowledge about the disease.

Intense biomedical research in the field of IT-IEM has resulted in substantial advances in treatment and a growing group of surviving patients (J. S. Cohen & Biesecker, 2010). These individuals have to cope with stressors such as strict diet, medication, crises management, and uncertainties about the future course of their disease and its consequences. Furthermore patients may have behavioural, cognitive, or psychiatric problems due to the CNS alterations caused by the disease (Walterfang et al., 2013), which again impair their psychological functioning (Dey, Landolt, & M., 2012; Fan, Eiser, & Ho, 2010). As a result, even though treatments have improved, IT-IEM affect the daily life and well-being of patients and their caregivers considerably (Weber, Segal, & Packman, 2012). Therefore, complementary research from a psychosocial perspective is especially needed (Gentile, Ten Hoedt, & Bosch, 2010; Weber et al., 2012).

Health-related quality of life (HrQoL), psychological adjustment, and adaptive functioning are well-established constructs to describe psychosocial consequences of chronic diseases. HrQoL has been defined as "a patient's perception of the impact of disease and treatment on functioning in a variety of dimensions, including physical, psychological and social domains" (Varni, Seid, & Rode, 1999, p. 126). Adjustment describes the healthy rebalancing of patients to a new condition (De Ridder, Geenen, Kuijer, & van Middendorp, 2008). We use the more specific term psychological adjustment to refer specifically to emotional, behavioural or social adjustment to a disease. Finally, adaptive functioning is a related term describing "the performance of daily activities required for personal and social sufficiency" (Sparrow, Cicchetti, & Balla, 2005, p. 6), consisting of the three domains conceptual, practical and social functioning (American Association on Mental Retardation (AAMR), 2002). To date, no consensus has arisen about how HrQoL, psychological adjustment, and adaptive functioning are affected in IT-IEM patients and what factors can influence the well-being of the patients. An overview of findings is lacking. For this reason, we decided to systematically review the current research on HrQoL, psychological adjustment, and adaptive functioning in IT-IEM patients. Our purpose was to answer two research questions:

(1) What is the current state of knowledge about self- and proxy-reported HrQoL, psychological adjustment, and adaptive functioning in IT-IEM patients?

(2) What are the medical and psychosocial risk factors for HrQoL, psychological adjustment, and adaptive functioning in IT-IEM patients?

1.3. Methods

Data sources and search strategies

To identify eligible studies for our review, we searched relevant databases with predefined search terms. The search was conducted using the following electronic bibliographic databases up to 30 April 2013: *Pubmed*, *Embase*, *Cinahl*, *PsycINFO, Psyndex* and the *Cochrane Database of Clinical Trials and Systematic Reviews*. *NDLTD (Networked Digital Library of Theses and Dissertations)* and *dissonline.de* were searched to find eligible dissertations. We applied two groups of search terms. Firstly, we employed various disease names referring to IEM and IT-IEM. Secondly, we referred to HrQoL, psychological adjustment, and adaptive functioning by employing these terms: quality of life, life satisfaction, well being, well-being, wellbeing, adjustment, adaption, adaptation, adaptive, psycholog*, psychosocial, psychiatr*, social, emotional, mental health, mental disorder, mental disease, behavior*, behaviour*. To augment the specificity of the search, the IEM / IT-IEM group and the HrQoL / psychological adjustment / adaptive functioning group were connected to

each other by the Boolean operator “AND”, whereas terms within the groups were connected by the Boolean operator “OR”. We also took advantage of other options to refine the search when the databases offered them; accordingly, search terms concerning IEM, HrQoL, psychological adjustment, and adaptive functioning were limited to titles and abstracts, and words with multiple possible endings or spellings were completed by wildcards. An additional search for studies was conducted in two ways. First, to minimise publication bias, experts in the field were contacted via e-mail and asked if they were aware of any relevant articles or unpublished data. In addition, the references of relevant articles were screened.

Study selection

To find eligible studies, we rated all the articles and dissertations found in our systematic search according to pre-defined inclusion and exclusion criteria. Studies were included if the number of participants was $N > 1$ and if the sample contained at least 50% IT-IEM patients or if the results of IT-IEM patients were reported separately. Outcomes had to include a self-, proxy, or examiner’s report of patients’ HrQoL, patients’ psychological adjustment (psychological, social, behavioural or emotional adjustment), or adaptive functioning. The assessment of these outcomes had to be completed in a standardised way and reported quantitatively. Reporting of methods and results had to be sufficient for replicability. Finally, reports were accepted if they were written in English, German, French or Spanish. Articles not fulfilling these criteria were excluded. The selection process was conducted in two major steps. First, one reviewer (N.A.Z.) examined all titles and abstracts. Second, studies that could not be excluded in the first examination were rated in their full-text version by two reviewers (N.A.Z. and M.H.) independently. Inter-rater reliability was substantial (Landis & Koch, 1977), with Cohen’s kappa = 0.79. Any disagreements were arbitrated through discussion. The remaining articles were included for data extraction.

Data extraction and analysis

Two reviewers (N.A.Z and M.A.L) extracted the data of the articles independently. Inter-rater reliability was almost perfect (Landis & Koch, 1977), with Cohen’s kappa = 0.98. Disagreements were resolved through discussion. The great variation between studies regarding design, such as measures and reporting of results, did not permit statistical pooling of data from the individual studies, so meta-analytic calculations were not possible. Instead, effect sizes were calculated whenever possible to attain some comparability between the results. Standardised mean differences, including 95% confidence intervals (CI), were calculated for continuous outcomes using Cohen’s d effect sizes, corrected for small sample sizes

(Durlak, 2009). An effect size was considered to be significant if its 95% CI did not include 0, thus considering a significance level of $p < .05$. According to Cohen's categories, an effect size is small if $d = 0.2 - 0.5$, medium if $d = 0.5 - 0.8$ and large if $d > 0.8$ (J. Cohen, 1988). Calculations were conducted such that a positive Cohen's d stands for a higher scoring of the IT-IEM group than of norms. Higher scorings are favourable for all scales, except for two cases: the Child Behaviour Checklist (CBCL) and the Behaviour Assessment System for Children (BASC) (all subscales but adaptive skills) report problem behaviour. Consequently, higher scores signify more problems and are unfavourable outcomes. For dichotomous outcomes, we used Chi-square tests, indicating the strength of the association by Cramer's V, with $p < .05$ considered significant. IBM SPSS Statistics for Windows, Version 20.0 was used for all calculations.

1.4. Results

The initial search of databases revealed 1669 articles and dissertations. After the first selection, 20 articles remained. During the second selection process, we had to exclude another nine articles; three were single-case reports, one had the same sample as another article included, and seven articles lacked standardised assessments of the patients' HrQoL, psychological adjustment, or adaptive functioning. One of these articles was a qualitative study (Packman et al., 2012). One additional, recently published article (Gramer et al., 2013) was found by contacting experts in the field, and another was traced (Mazariegos et al., 2012) by screening the references of relevant studies. The search and selection process is depicted in Figure 1. Finally, 11 articles remained for further analyses.

Study description

The main characteristics and results of the articles included in our review are summarised in Table 1. Further information about the assessment instrument used in the studies can be found in Table 2. Detailed analyses of outcome parameters are shown in Tables 3 and 4. All 11 articles were published between 2006 and 2013, seven of them in 2012 or 2013. Four articles have their origins in the United States, two in Germany and one each in Australia, Belgium, Italy, Poland and Turkey. All articles are written in English. All of the four disease groups we searched for (UCD, OA, MSUD, TYR 1) are represented in the final selection of studies. Patients diagnosed with MSUD (n = 124) represent the largest group, followed by OA (n =107), UCD (n = 100) and TYR 1 (n = 11). Seven studies reported outcomes for only one of these disease groups, four studies included patients of multiple groups. From six articles, only subgroup data were extracted. In four studies, we selected IT-IEM patients from

the original samples, which integrated patients with IT-IEM and patients with other diseases (Cazzorla et al., 2012; Eminoglu, Soysal, Tumer, Okur, & Hasanoglu, 2013; Gramer et al., 2013; Simons et al., 2006). One study reported on IT-IEM patients before and after transplantation. Only the subgroup before transplantation was selected for further analysis (Muelly et al., 2013). In another study, outcome regarding adaptive functioning was only available for a subgroup (Mazariegos et al., 2012). The final sizes considered ranged from N = 4 to N = 92 patients.

Many of the studies had methodological limitations. One main weakness is the lack of appropriate participant selection (i.e. use of convenience samples) in order to avoid selection or non-response bias (Beauchamp, Boneh, & Anderson, 2009; Cazzorla et al., 2012; Eminoglu et al., 2013; Grünert et al., 2013; Krivitzky et al., 2009; Muelly et al., 2013; Packman et al., 2007; Pohorecka et al., 2012). Two studies involved a non-validated measuring tool (Eminoglu et al., 2013; Gramer et al., 2013). Furthermore, only two studies considered multiple informants in terms of self- and proxy-ratings (Packman et al., 2007; Simons et al., 2006).

Table 1: Main characteristics of the reviewed studies

Author, year *(origin)*	**Metabolic disease**	**N***	**Reviewed sample vs. originally reported sample**	**Mean age in years (range)**	**Group of comparison**	**Assessment instrument* *(report)***	**Selected results*** (IT-IEM related to group of comparison)**
Beauchamp et al., 2009 *(Australia)*	GA I	4	Same	5.8 (5 to 7)	Population norms	• CBCL *(proxy-mother)* • ABAS *(proxy-mother)*	• **Psychological adjustment (CBCL):** No sign. group difference, except for CBCL total scale, where IT-IEM patients show less behavioural problems than the norm population (doubt about reliability of this result) • **Adaptive functioning (ABAS):** No sign. group difference
Cazzorla et al., 2012 *(Italy)*	OTCD, HHH Syndrome, ASA, GA I, MMA, MSUD	15	*Reviewed sample:* only IT-IEM *Orig. sample:* IT-IEM mixed with other diseases (N = 82)	25.6 (17 to 44)	Population norms, other IEM-groups (PKU, Morbus Fabry, pharmacological treatment)	• WHOQOL-100 *(self)*	• **QoL (WHOQOL-100):** Compared to population norms: sign. higher QoL for physical domain, lower for environmental domain, no sign. group difference for all other domains • **QoL (WHOQOL-100):** Compared to other IEM: no sign. group difference compared to PKU for all domains, sign. higher compared to Morbus Fabry and pharmacologically treated patients in most domains (no sign. group difference for social and environmental domains)

Table 1: Main characteristics of the reviewed studies (continued)

Eminoglu et al., 2013 *(Turkey)*	MA, PA, MSUD, TYR *(group includes n = 3 patients with a disease not being an IT-IEM)*	14	*Reviewed sample:* separately reported subgroup, mainly IT-IEM, 3 other IEM *Orig. sample:* IT-IEM mixed with other IEM (N = 68)	4.7 (n.a., SD = 4.3)	Population norms, other IEM-groups: CMD and AMD	• Questionnaire constructed by authors: QoL Scale for Metabolic Diseases *(proxy-parent)* • Kiddy-, Kid-Kiddo-KINDL *(proxy-parent, self if >= 4years)*	• **HrQoL (QoL Scale for Metabolic Diseases):** Sign. lower compared to CMD and AMD for school status and health perception domains, sign. Lower in physical function domain compared to AMD, similar for other domains • **HrQoL (KINDL):** No sign. group difference compared to CMD and AMD for emotional wellbeing domain
Gramer et al., 2013 *(Germany)*	ASLD, GA I, IVA, PA, MSUD	34	*Reviewed sample:* only IT-IEM *Orig. sample:* IT-IEM mixed with other IEM (N = 187)	4 (1.2 to 9.7)	None	Questionnaire constructed by authors, assessing*:* • Perceived burden for the child *(proxy-parent)* • Social behavior *(proxy-parent)*	• **Psychological adjustment (Perceived burden for the child):** Rated as low for the majority (50%) • **Psychological adjustment (Social behaviour):** Rated average for the majority (82%)
Grünert et al., 2013 *(Germany)*	PA	48	Same	5 (5days to 19) • For Kid-Kindl: 11 (5 to 18) • For SDQ: 4 (1 to 18)	Population norms	• Kid-KINDL *(self): n = 18* • SDQ *(proxy-parent)*: n = 48 n according to age or degree of mental retardation	• **HrQoL (KINDL):** Sign. Lower HrQoL for psychological and friends domain, sign. higher for school domain, no group difference for other domains • **Psychological adjustment (SDQ):** More problems in all scales except conduct problems

Table 1: Main characteristics of the reviewed studies (continued)

Krivitzky et al., 2009 *(USA)*	UCD	92	Same	7.2 (0.4 to 16.75)	Population norms	• ABAS (proxy-parent): all ages • CBCL (proxy-parent): for ages 3-16	• **Adaptive functioning (ABAS):** General score was sign. lower for all IT-IEM groups (neonatal onset, late onset, patients with / without hyperammonemic history) in the age of 3-16 years • **Adaptive functioning (ABAS):** General score was sign. lower for the IT-IEM patients with a hyperammonemic history, not for the other subgroups, in the age group of < 3 years • **Psychological adjustment (CBCL):** No sign. group difference in internalising and externalising problems
Mazariegos et al., 2012 *(USA)*	MSUD	31	*Reviewed sample:* Patients with results for adaptive functioning*Orig. sample:* Patients with and without results for adaptive functioning (N = 35)	9.9 (1.7 to 32.1) (for N = 35)	Population norms	• ABAS *(self)* or Vineland *(self)* (for this review: only pre-transplantation assessment)	• **Adaptive functioning (ABAS or Vineland):** Sign. lower score for adaptive functioning• **Risk factor assessment:** Sign positive correlation between IQ and adaptive function• **Risk factor assessment:** No sign. correlation between adaptive test scores and age at diagnosis, number of preceding metabolic crises, number of hospitalizations, age at transplantation

Table 1: Main characteristics of the reviewed studies (continued)

Muelly et al., 2013 *(USA)*	MSUD	26	*Reviewed sample:* IT-IEM patients on diet, not liver-transplanted *Orig. sample:* IT-IEM patients on diet and IT-IEM after liver transplantation (N = 37)	• For MSUD diet n = 26: n.a., Mdn = 19.5 (7 to 35) • For controls n = 26: n.a., Mdn = 15.9 (6 to 35)	Healthy control group (mostly siblings of MSUD-patients)	• SCID *(adult or childhood version)* for DSM-IV: depression, anxiety, ADHD, global, social, occupational and psychological functioning *(self)* • BDI and BAI or sub-scores of the BYI of emotional and social Impairment *(self)*	• **Psychological adjustment (Severity of depression and Anxiety, BDI, BAI, BYI):** No sign. group difference • **Psychological adjustment (Current and lifetime depression and anxiety, DSM-IV):** Sign. more lifetime depression and anxiety • **Risk factor assessment:** Patient who remained asymptomatic throughout newborn period vs. patients who were encephalopathic at the time of diagnosis: Second group has higher risk to later suffer from anxiety (5x higher) and for depression (10x higher) • **Risk factor assessment:** Correlation of mood disturbances with some biochemical parameters. No strong correlation of depression and anxiety with indices of lifetime metabolic control

Table 1: Main characteristics of the reviewed studies (continued)

Packman et al., 2007 (*USA)*	MSUD	55	Same	11 (5 to 18)	Population norms	• BASC *(proxy-parent, proxy-teacher)* • PedsQL *(self, proxy-parent)*	• **HrQoL (PedsQL):** Total HrQoL score and domains are closer to cancer sample norms than to healthy sample norms • **Psychological adjustment and adaptive functioning (BASC):** Mostly no sign. group difference. Sign. more problems in some areas, sign. lower scores in adaptive skills (parent- and teacher-rating) • **Self- vs. proxy-rating:** HrQoL self-report > proxy-report for physical, emotional, social domain, no difference for school function • **Self- vs. proxy-rating:** Behavioural adjustment proxy parent- vs. proxy teacher-report: parent < teacher for internalising problems (somatization, anxiety)
Pohorecka et al., 2012 *(Poland)*	TYR I	8	Same	11 (6 to 15)	Population norms	• CBCL *(proxy-parent)*	• **Psychological adjustment (CBCL):** Sign. more problems in several scales
Simons et al., 2006 *(Belgium)*	OTCD, GA III, MMA	11	*Reviewed sample:* only IT-IEM *Orig. sample:* IT-IEM mixed with other IEM (N = 53)	n.a. (0-2 to 16) (for N = 53)	Population norms	• CBCL, TRF, YSR *(proxy-parent, proxy-teacher, self if child > 11years old)* • K-SADS for DSM-IV diagnosis *(self)*	• **Psychological adjustment (CBCL):** No sign. group difference • **Psychological adjustment (DSM-IV):** Psychiatric diagnoses in n = 2, but scale was not applied to the whole sample

* The N reported corresponds to the highest number of participants for which HrQoL / psychological outcome is reported.

** Results are based on the statistic analysis done for this review. A "significant" outcomes means that the calculated 95% CI of the effect size does not include the value of zero and is thus on a level of $p < 0.05$ (continuous results) or that the χ^2-test revealed a significant result on a level of $p < 0.05$ or lower (dichotomous results). The statements refer to IT-IEM patients related to the respective group of comparison.

Table 1: Main characteristics of the reviewed studies (continued)

Abbreviations diseases: AMD (Amino Acid Metabolism Disorders), ASA (Arginosuccinic Aciduria), ASLD (Adenylosuccinate Lyase Deficiency), CMD (Carbohydrate Metabolism Disorders), GA I (Glutaric Aciduria type I), GA III (Glutaric Aciduria type III), HHH Syndrom (Hyperornithinemia-Hyperammonemia-Homocitrullinuria Syndrome), IEM (Inborn Errors of Metabolism), IVA (Isovaleric Aciduria), IT-IEM (Intoxication-type Inbron Errors of Metabolism), MMA (Methylmalonic Aciduria), MSUD (Maple Syrup Urine Disease), OTCD (Ornithintranscarbamylase Deficiency), PA (Propionic Aciduria), TYR I (Tyrosinemia type I), UCD (Urea Cycle Disorder)

Abbreviations assessment instruments: ABAS (Adaptive Behaviour Assessment System), BAI (Beck Anxiety Inventory), BASC (Behaviour Assessment System for Children), BDI (Beck Depression Inventory), BYI (Beck Youth Inventory), CBCL (Child Behaviour Check List) with YSF (Youth-report form) and TRF (Teacher-report form), DSM-IV (Diagnostic and Statistical Manual of Mental Disorders IV), Kiddy-, Kid-, Kiddo-KINDL (Revised questionnaire to assess health-related quality of life in children and adolescents), K-SADS (Schedule for Affective Disorders and Schizophrenia for School-Age Children), PedsQL (Pediatric Quality of Life Inventory), SDQ (Strengths and Difficulties Questionnaire), SCID (Structured clinical interview for DSM-IV), Vineland (Vineland Adaptive Behavior Scale), WHOQOL-100 (World Health Organisation Quality of Life assessment)

Table 2: Overview of assessment instruments used in the reviewed studies

Assessment Instrument		General use	Reference
ABAS	Adaptive Behaviour Assessment System	Assessment of adaptive behaviour and skills necessary for daily living, for individuals from birth to 89 years. Thirteen scales are organised in three general areas: conceptual, social, practical. Versions for self- and different proxy-reports are available.	Harrison, PL, Oakland, T (2003). *Adaptive Behavior Assessment System - Second Edition.* San Antonio, TX: The Psychological Corporation.
BAI	Beck Anxiety Inventory	Assessment of severity of anxiety of individuals aged from 17 to 80 years. Consists of 21 multiple choice questions for self-report.	Beck, A, Steer, R (1993). *Manual for the Beck Anxiety Inventory.* San Antonio, Texas, USA: The Psychological Coorporation Harchourt Brace & Company; 1993.
BASC	Behaviour Assessment System for Children	Assessment of behaviour and self-perception of children aged from 2 years 6 months to 18 years. Teacher-, parent- and self-report versions available.	Reynolds CR, Kamphaus RW: *Behavior assessment system for children.* Circle Pines, MN: American Guidance Service 1992.
BDI	Beck Depression Inventory	Assessment of severity of depression of individuals aged from 13 to 80 years. Consists of 21 multiple choice questions for self-report.	Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J: **An inventory for measuring depression.** *Arch Gen Psychiatry* 1961, **4:**561-571.
BYI	Beck Youth Inventory	Consisting of five inventories (anger, anxiety, depression, disruptive behaviour, self-concept) for children and adolescents aged from 7 to 17 years. Each inventory consists of 20 questions for self-report.	Beck, J, Beck, A, Jolly, J (2001). Beck Youth Inventories of Emotional and Social Impairment. San Antonio, Texas USA: The Psychological Coorporation.

Table 2: Overview of assessment instruments used in the reviewed studies (continued)

CBCL	Child Behaviour Check List	Ratings of behavioural, emotional and social functioning of children and adolescents aged from 1 year 6 month to 18 years. Behaviours are categorized into internalising problem scales (e.g. anxiety, somatic complaints) and externalising problem scales (e.g. aggressive behaviour, attention problems). The CBCL is for parent-report, a teacher-report form (TRF) and a youth-report form (YRF) are available.	Achenbach, TM, & Rescorla, LA (2000). *Manual for the ASEBA Preschool Forms & Profiles.* Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families.
KINDL	Revised questionnaire to assess health-related quality of life in children and adolescents	Generic instrument to assess health-related quality of life in children and adolescents aged from 3 to 17 years. Version for three age groups are available (Kiddy-, Kid-, Kiddo-KINDL), each in self- and proxy-rating. Dimensions: psychological well-being, social relationships, physical function, everyday life activities	Ravens-Sieberer U, Bullinger M: **Assessing health-related quality of life in chronically ill children with the German KINDL: first psychometric and content analytical results.** *Qual Life Res* 1998, **7:**399-407.
K-SADS	Schedule for affective disorders and schizophrenia for school-age children	Semi-structured interview to make DSM-IV (Diagnostic and Statistical Manual of Mental Disorders IV) diagnoses in children and adolescents from aged from 6 to 16 years. Answers from parents and children are both considered.	Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, Williamson D, Ryan N: **Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data.** *J Am Acad Child Adolesc Psychiatry* 1997, **36:**980-988.
PedsQL	Pediatric Quality of Life Inventory	Assessment of health-related quality of life in children and adolescents aged from 2 to 18 years. Can be used in healthy individuals (generic module) and in those with health conditions (additional disease-specific modules). Self- and proxy-report versions are available. Consists of 23 items forming the generic module. Disease-specific modules are available e.g. for asthma, diabetes, cancer. Scales: Physical, emotional, social and school functioing.	Varni JW, Seid M, Rode CA: **The PedsQL: measurement model for the pediatric quality of life inventory.** *Med Care* 1999, **37:**126-139.

Table 2: Overview of assessment instruments used in the reviewed studies (continued)

SCID	Structured clinical interview for DSM-IV	Semi-structured interview to make DSM-IV (Diagnostic and Statistical Manual of Mental Disorders IV) diagnoses in adults, version for children is available.	First MB, Spitzer, RL, Gibbon, M, Williams, JBW: *Structured clinical interview for DSM-IV_TR Axis I Disorders, Research Version, Non-Patient Edition*. New York, NY: Biometrics Research, New York State Psychiatric Institute; 2002.
SDQ	Strengths and Difficulties Questionnaire	Instrument to screen behavioural strengths and difficulties in children and adolescents aged from 3-16 years. Parent- or teacher-report, available in self-report for 11-16 year olds. 25 Items for 5 scales: emotional symptoms, conduct problems, hyperactivity / inattention, peer relationship problems, prosocial behaviour.	Goodman R: **The Strengths and Difficulties Questionnaire: a research note.** *J Child Psychol Psychiatry* 1997, **38:**581-586.
Vineland	Vineland Adaptive Behavior Scale	Assessment of adaptive behaviour and skills necessary for daily living from birth to 90 years. Scales refer to functions necessary for daily living and are organised in three main areas: Communication, daily living skills, socialization. Self-, caregiver- and teacher-rating forms are available.	Sparrow SS, Cicchetti, DV, Balla, DA: *Vineland Adaptive Behavior Scales*. Circle Pines, MN: AGS Publishing; 2005.
WHOQOL-100	World Health Organisation Quality of Life assessment	Instrument to assess subjective quality of life in adults. Self- and proxy-report version available. Dimensions: physical, psychological, independence, social, environment, religion/spirituality.	The WHOQOL Group: **The World Health Organization Quality of Life Assessment (WHOQOL): development and general psychometric properties.** *Soc Sci Med* 1998, **46:**1569-1585.

Findings on HrQoL

Self-report

As shown in Table 3, results for self-reported HrQoL are inconsistent across studies. In one study, the authors reported significantly lower HrQoL for IT-IEM patients in most domains compared to population norms (Packman et al., 2007). The results for IT-IEM patients were closer to the results of a cancer population than to a healthy one. Two other studies showed results with more variance throughout the different HrQoL domains. One study reported clearly lower scores for IT-IEM patients than for population norms in the *psychological* and the *friends domain*s, but higher scores for the *school domain* (Grünert et al., 2013). The results for other domains did not differ from norms. Half of the patients in the sample of this study did not categorise themselves as "ill". In contrast, another group of researches reported significantly better scores in the *physical domain* for IT-IEM patients compared to population norms (Cazzorla et al., 2012), but lower scores in the *environmental domain* (including e.g. financial resources, health care, physical environment). The same study found HrQoL of IT-IEM patients to be similar to that of patients with phenylketonuria, who also have to follow a strict diet but who do not face the risk of sudden metabolic crises. Furthermore, IT-IEM patients had higher HrQoL in most domains compared to Morbus Fabry patients, who often have to deal with pain symptoms, and patients with metabolic diseases under pharmacological (as opposed to dietary) treatment (Cazzorla et al., 2012).

Proxy-report

Proxy-ratings of HrQoL were all reported by parents. All results for IT-IEM patients were either not different from norms or unfavourable for IT-IEM patients (Table 3). One study showed significantly lower parent-rated HrQoL for IT-IEM patients across all domains compared to population norms (Packman et al., 2007). In line with the results for self-reported HrQoL in the same study, the results were closer to cancer population norms than to healthy norms. *Psychosocial* and *social domains* were lower in IT-IEM patients than in the cancer population. In another article, the parent-rated HrQoL of IT-IEM patients was compared with the parent-rated HrQoL of patients with other metabolic diseases (aminoacid metabolic disorders and carbohydrate metabolic disorders) (Eminoglu et al., 2013). IT-IEM patients scored lower in the domains of *school functioning*, *health perception* (compared with both diseases) and *physical functioning* (only compared with aminoacid metabolic disorders).

Table 3: Continuous outcomes in the reviewed studies

Reference				CI of d			
N	**Instrument**	**Subscale**	**ES[1]: Cohen's d**	**lower**		**upper**	**sign.**
Health-related quality of life: self-report							
			Compared to population norms				
Cazzorla et al., 2012	WHOQOL-100	General	n.a.	n.a.	to	n.a.	n.a.
N = 15		Physical	0.62	0.10	to	1.13	*
		Psychological	0.52	0.00	to	1.04	ns
		Independence	n.a.	n.a.	to	n.a.	n.a.
		Social	-0.13	-0.64	to	0.39	ns
		Environmental	-2.43	-2.97	to	-1.89	*
		Spiritual	n.a.	n.a.	to	n.a.	n.a.
		Medication	n.a.	n.a.	to	n.a.	n.a.
			Compared to PKU				
		General	0.03	-0.69	to	0.74	ns
		Physical	0.16	-0.56	to	0.88	ns
		Psychological	0.70	-0.04	to	1.44	ns
		Independence	-0.34	-1.06	to	0.38	ns
		Social	0.14	-0.58	to	0.85	ns
		Environmental	0.41	-0.31	to	1.14	ns
		Spiritual	0.31	-0.41	to	1.04	ns
		Medication	0.70	-0.04	to	1.44	ns
			Compared to Morbus Fabry				
		General	1.15	0.35	to	1.95	*
		Physical	1.49	0.65	to	2.33	*
		Psychological	0.90	0.12	to	1.68	*
		Independence	1.11	0.31	to	1.90	*
		Social	0.70	-0.06	to	1.47	ns
		Environmental	0.91	0.13	to	1.69	*
		Spiritual	1.07	0.28	to	1.87	*
		Medication	-0.35	-1.10	to	0.40	ns
			Compared to IEM with pharmacological treatment				
		General	0.92	0.27	to	1.56	*
		Physical	1.19	0.53	to	1.86	*
		Psychological	0.94	0.30	to	1.59	*
		Independence	0.74	0.11	to	1.38	*
		Social	0.16	-0.46	to	0.78	ns
		Environmental	0.75	0.12	to	1.39	*
		Spiritual	0.90	0.25	to	1.54	*
		Medication	-0.26	-0.88	to	0.36	ns
			Compared to population norms				
Grünert et al., 2013	KINDL	Total	-0.34	-0.81	to	0.12	ns
N = 18		Physical	-0.28	-0.74	to	0.19	ns
		Psychological	-0.78	-1.25	to	-0.32	*

Table 3: Continuous outcomes in the reviewed studies (continued)

		Self-esteem	0.15	-0.32	to	0.63	ns
		Family	-0.38	-0.84	to	0.09	ns
		Friends	-0.68	-1.14	to	-0.21	*
		School	0.73	0.22	to	1.24	*
		Illness	n.a.	n.a.	to	n.a.	n.a.
			Compared to healthy population norms				
Packman et al., 2007	PedsQL self-report	Physical function	-0.28	-0.69	to	0.13	ns
N = 55		Emotional function	-0.55	-0.96	to	-0.14	*
		Social function	-0.80	-1.22	to	-0.39	*
		School function	-0.70	-1.12	to	-0.29	*
		Psychosocial	-0.85	-1.27	to	-0.44	*
		Total	-0.77	-1.19	to	-0.36	*
			Compared to cancer population norms				
		Physical function	0.42	0.00	to	0.84	ns
		Emotional function	-0.04	-0.46	to	0.38	ns
		Social function	-0.24	-0.66	to	0.19	ns
		School function	-0.24	-0.67	to	0.18	ns
		Psychosocial	-0.23	-0.65	to	0.19	ns
		Total	-0.02	-0.44	to	0.40	ns
Health-related quality of life: proxy-report							
			Compared to CMD				
Eminoglu et al., 2013	QOL Scale for Metabolic Disease	Impact of IEM	-0.18	-1.02	to	0.67	ns
N = 14		Attention	-0.42	-1.15	to	0.31	ns
		Self-esteem about IEM	0.03	-0.70	to	0.76	ns
		Physical function	-0.65	-1.38	to	0.08	ns
		Labeling	-0.57	-1.41	to	0.27	ns
		Social support	0.17	-0.69	to	1.03	ns
		School status	-0.93	-1.77	to	-0.09	*
		Health perception	-1.69	-2.64	to	-0.74	*
	KINDL	Emotional wellbeing	-0.44	-1.07	to	0.19	ns
			Compared to AMD				
	QOL Scale for Metabolic Disease	Impact of IEM	-0.24	-1.18	to	0.69	ns
		Attention	-0.64	-1.43	to	0.16	ns
		Self-esteem about IEM	-0.45	-1.26	to	0.36	ns
		Physical function	-1.14	-1.96	to	-0.33	*
		Labeling	-0.15	-1.02	to	0.71	ns
		Social support	-0.55	-1.47	to	0.38	ns
		School status	-1.41	-2.41	to	-0.40	*
		Health perception	-1.67	-2.70	to	-0.64	*
	KINDL	Emotional wellbeing	-0.20	-0.88	to	0.48	ns
			Compared to population norms				
	QOL Scale for Metabolic Disease		n.a.	n.a.	to	n.a.	n.a.
	KINDL		n.a.	n.a.	to	n.a.	n.a.

Table 3: Continuous outcomes in the reviewed studies (continued)

			Compared to healthy population norms				
Packman et al., 2007	PedsQL proxy-report	Physical function	-1.14	-1.54	to	-0.74	*
N = 55		Emotional function	-1.19	-1.59	to	-0.80	*
		Social function	-1.48	-1.88	to	-1.08	*
		School function	-1.46	-1.86	to	-1.06	*
		Psychosocial	-1.66	-2.06	to	-1.26	*
		Total	-1.65	-2.05	to	-1.25	*
			Compared to cancer population norms				
		Physical function	-0.06	-0.46	to	0.34	ns
		Emotional function	-0.23	-0.63	to	0.17	ns
		Social function	-0.65	-1.05	to	-0.25	*
		School function	-0.39	-0.80	to	0.01	ns
		Psychosocial	-0.54	-0.94	to	-0.14	*
		Total	-0.40	-0.80	to	0.00	ns
Psychological adjustment and adaptive functioning: self-report							
			Compared to population norms				
Muelly et al., 2013	BDI / BYI	BDI score adults	0.54	-0.02	to	1.11	ns
N = 26		BYI T-score	-0.44	-1.01	to	0.12	ns
		Combined z-score	0.19	-0.36	to	0.75	ns
	BAI / BYI	BAI score adults	0.38	-0.18	to	0.94	ns
		BYI T-score	-0.28	-0.83	to	0.28	ns
		Combined z-score	0.13	-0.43	to	0.68	ns
			Compared to population norms				
Mazariegos et al., 2012	Vineland or ABAS	Total	-1.09	-1.46	to	-0.72	*
N = 31							
Psychological adjustment and adaptive functioning: proxy-report							
			Compared to population norms				
Beauchamp et al., 2009	CBCL	Internalising problems	-0.32	-1.31	to	0.66	ns
N = 4		Externalising problems	-0.76	-1.74	to	0.23	ns
		Total	-1.32	-2.31	to	-0.34	*
	ABAS	General score	-0.23	-1.21	to	0.75	ns
		Conceptual	-0.65	-1.63	to	0.34	ns
		Social	0.84	-0.14	to	1.82	ns
		Practical	-0.50	-1.48	to	0.48	ns
			Neonatal onset vs. population norms				
Krivitzky et al., 2009	ABAS, age < 3 y	General score	-0.35	-0.83	to	0.13	ns
N = 92	ABAS, age 3-16y	General score	-2.09	-2.64	to	-1.53	*
			Late onset vs. population norms				
	ABAS, age < 3 y	General score	-0.67	-1.42	to	0.07	ns
	ABAS, age 3-16y	General score	-0.76	-1.04	to	-0.47	*

Table 3: Continuous outcomes in the reviewed studies (continued)

			Hyp.amm. events >= 0 vs. population norms			
	ABAS, age < 3 y	General score	-0.37	-0.88	to	-0.37	*
	ABAS, age 3-16y	General score	-1.00	-1.33	to	-0.99	*
			Hyp.amm. events = 0 vs. population norms			
	ABAS, age < 3 y	General score	-0.55	-1.20	to	0.11	ns
	ABAS, age 3-16y	General score	-0.96	-1.36	to	-0.56	*
			Compared to population norms			
Packman et al., 2007	BASC parent-report	Hyperactivity	0.26	-0.03	to	0.55	ns
N = 55		Aggression	0.24	-0.04	to	0.53	ns
		Conduct problems	0.03	-0.25	to	0.32	ns
		Anxiety	0.05	-0.24	to	0.34	ns
		Depression	0.08	-0.21	to	0.36	ns
		Somatization	0.21	-0.08	to	0.50	ns
		Atypicality	0.30	0.01	to	0.59	*
		Withdrawal	0.04	-0.24	to	0.33	ns
		Attention problems	0.68	0.39	to	0.97	*
		Externalising problems	0.21	-0.08	to	0.50	ns
		Internalising problems	0.14	-0.15	to	0.43	ns
		Behavioral sympt. index	0.37	0.08	to	0.66	*
		Adaptive skills	-0.59	-0.88	to	-0.30	*
			Compared to population norms			
	BASC teacher-report	Hyperactivity	0.41	0.07	to	0.76	*
		Aggression	0.28	-0.07	to	0.62	ns
		Conduct problems	-0.18	-0.52	to	0.16	ns
		Anxiety	0.55	0.20	to	0.89	*
		Depression	0.11	-0.23	to	0.45	ns
		Somatization	0.66	0.32	to	1.01	*
		Attention problems	0.75	0.41	to	1.10	*
		Learning problems	0.74	0.39	to	1.08	*
		Atypicality	0.68	0.34	to	1.03	*
		Withdrawal	0.19	-0.15	to	0.53	ns
		Externalising problems	0.23	-0.12	to	0.57	ns
		Internalising problems	0.56	0.21	to	0.90	*
		School problems	0.76	0.42	to	1.11	*
		Behavioral sympt. index	0.62	0.28	to	0.97	*
		Adaptive Skills	-0.36	-0.71	to	-0.02	*
			Compared to population norms			
Pohorecka et al., 2012	CBCL	Internalising problems	1.14	0.44	to	1.84	*
N = 8		Externalising problems	0.77	0.08	to	1.47	*
		Withdrawn	1.30	0.60	to	2.01	*
		Somatic complaints	1.19	0.49	to	1.90	*
		Anxious depressed	0.62	-0.08	to	1.32	ns
		Social problems	1.52	0.82	to	2.23	*
		Thought problems	0.89	0.19	to	1.59	*
		Attention problems	1.15	0.45	to	1.86	*

Table 3: Continuous outcomes in the reviewed studies (continued)

		Rule breaking behaviour	1.07	0.37	to	1.77	*
		Aggressive behaviour	0.86	0.16	to	1.56	*
			Compared to population norms				
Simons et al., 2006	CBCL	Internalising problems	0.79	-0.02	to	1.59	ns
N = 11		Externalising problems	0.36	-0.44	to	1.17	ns
		Total	0.64	-0.17	to	1.44	ns

[1]A positive value means that the IT-IEM group scored higher than the control group. A negative value means that the IT-IEM group group lower than the control group. Higher values are favourable in all scales except for the BASC (Packman et al.) where high scores mean more problems (exception: BASC subscale adaptive skills).

Abbreviations: ABAS (Adaptive Behaviour Assessment System), BAI (Beck Anxiety Inventory), BASC (Behaviour Assessment System for Children), BDI (Beck Depression Inventory), BYI (Beck Youth Inventory), CBCL (Child Behaviour Check List), KINDL (Revised questionnaire to assess health-related quality of life in children and adolescents), PedsQL (Pediatric Quality of Life Inventory), Vineland (Vineland Adaptive Behavior Scale), WHOQOL-100 (World Health Organization Quality of Life assessment)

Self- vs. proxy-report

One study (Packman et al., 2007) compared self- and parent proxy-ratings. The authors reported significantly better scores in self-reported HrQoL for the domains of *physical*, *emotional* and *social* HrQoL, but no difference for *school functioning*.

Risk factors

No risk factors regarding HrQoL were investigated in the studies.

Findings on psychological adjustment and adaptive functioning

Self-report

Results for self-reported psychological adjustment and adaptive functioning are shown in Tables 3 and 4. Depression and anxiety (both current and lifetime) were reported to be more prevalent in a group of IT-IEM patients than in a healthy group (Muelly et al., 2013). However, the study revealed no differences between IT-IEM patients and population norms regarding anxiety and depression symptom severity. Another research group found adaptive functioning for IT-IEM patients to be significantly lower than in a norm population (Mazariegos et al., 2012).

Proxy-report

All studies used parent proxy-reports and one additionally used teacher proxy-reports (Tables 3 and 4). Proxy-report findings on different aspects of psychological adjustment and adaptive functioning mostly showed either no difference or worse adjustment and more problems for IT-IEM patients than norms (Grünert et al., 2013; Krivitzky et al., 2009; Packman et al., 2007; Pohorecka et al., 2012; Simons et al., 2006). Fewer problems compared to population norms were described in one paper (Beauchamp et al., 2009).

Proxy-parent vs. proxy-teacher-report

According to one study, teachers reported more *internalising problems* (*somatisation*, *anxiety*) than parents (Packman et al., 2007).

Risk factors

For psychological adjustment and adaptive functioning parameters, several risk factors were investigated. The risk for *lifetime anxiety* or *lifetime depression disorders* was higher in patients who were encephalopathic at diagnosis than patients who were non-symptomatic at diagnosis (Muelly et al., 2013). Adaptive functioning correlated with IQ according to another study, but no correlation was found between adaptive functioning and age at diagnosis, number of preceding metabolic crises, or number of hospitalisations (Mazariegos et al., 2012). Finally, lower scores in adaptive functioning were found among patients with neonatal onset than among late-onset patients, but no difference was found in the number of hyperammonemic events (Krivitzky et al., 2009)

Table 4: Dichotomous outcomes in the reviewed studies

Reference N	Instrument	Subscale	n IT-IEM	n con- trol	Results	Test of between group significance	Cramer's V
Psychological adjustment, self-report							
					% present IT-IEM / % present control	**Compared to healthy control group**	
Muelly et al., 2013 N = 26	SCID, DSM-IV	Depression current	26	26	29/4	χ^2 = 22.68; *df* = 1; *p* (2-tail) = 0.000 (***)	0.34
		Depression lifetime	26	26	42/19	χ^2 = 12.48; *df* = 1; *p* (2-tail) = 0.000 (***)	0.25
		Anxiety current	26	26	42/15	χ^2 = 17.89; *df* = 1; *p* (2-tail) = 0.000 (***)	0.30
		Anxiety lifetime	26	26	58/31	χ^2 = 14.96; *df* = 1; *p* (2-tail) = 0.000 (***)	0.27
Psychological adjustment, proxy-report							
					n IT-IEM in different categories (n control n.a.)	**No group of comparison**	
Gramer et al., 2013 N = 34		Perceived burden for the child	34	none	No (n = 5), little (n = 17), middle (n = 5), heavy (n = 4), very heavy (n = 3)	n.a.	n.a.
		Social behaviour	34	none	Lower than norm (n = 3), same as norm (n = 28), higher than norm (n = 3)	n.a.	n.a.
					% normal / at risk / clinically sign. IT-IEM (% normal / at risk / clinically sign. control)	**Compared to population norms**	
Grünert et al., 2013	SDQ	Emotional symptoms	48	930	62/13/25 (84/7/9)	χ^2 = 12.64; *df* = 2; *p* (2-tail) = 0.002 (**)	0.25

Table 4: Dichotomous outcomes in the reviewed studies (continued)

N = 48		Conduct problems	46	930	54/26/20 (69/16/15)	χ^2 = 4.93; *df* = 2; *p* (2-tail) = 0.085 (ns)	0.15
		Hyperactivity/Inattention	47	930	62/28/10 (86/6/8)	χ^2 = 18.35; *df* = 2; *p* (2-tail) = 0.000 (***)	0.30
		Peer relationship problems	46	930	39/20/41 (78/11/12)	χ^2 = 32.92; *df* = 2; *p* (2-tail) = 0.000 (***)	0.40
		Prosocial behaviour	47	930	57/9/34 (89/7/4)	χ^2 = 30.95; *df* = 2; *p* (2-tail) = 0.000 (***)	0.39
		Influence on child's life	48	930	60/11/29 (n.a.)	n.a.	n.a.
		Total	46	930	52/20/28 (85/8/7)	χ^2 = 25.69; *df* = 2; *p* (2-tail) = 0.000 (***)	0.36
					% normal / at risk / clinically sign. IT-IEM (% normal / at risk / clinically sign. control)	**Compared to population norms**	
Krivitzky et al., 2009	CBCL	Internalising problems	68	576	79/17/4 (83/7/11)	χ^2 = 5.87; *df* = 2; *p* (2-tail) = 0.053 (ns)	0.17
N = 92		Externalising problems	68	576	80/16/4 (83/7/11)	χ^2 = 5.26; *df* = 2; *p* (2-tail) = 0.072 (ns)	0.16

Abbreviations: CBCL (Child Behaviour Check List), DSM-IV (Diagnostic and Statistical Manual of Mental Disorders IV), SCID (Structured Clinical Interview for DSM-IV), SDQ (Strengths and Difficulties Questionnaire)

1.5. Discussion

HrQoL, psychological adjustment, and adaptive functioning

The first aim of our systematic review was to explore the current state of research on HrQoL, psychological adjustment, and adaptive functioning in patients with IT-IEM. We found 11 articles reporting HrQoL, psychological adjustment, or adaptive functioning for this group of patients. Results for HrQoL varied across studies from lower HrQoL to similar and better scores for IT-IEM patients compared to norms. Notably, proxy-ratings of patients' HrQoL were consistently similar or lower than norms. Results for psychological adjustment and adaptive functioning varied less and were mostly comparable to norms or showed worse adjustment for IT-IEM patients. Fewer problems were only reported once (Beauchamp et al., 2009) – however, this result has to be considered with care. The sample size of this study was very small (n = 4) compared to the other studies, and the authors themselves expressed some doubts about the reliability of their results.

Impaired HrQoL, psychological adjustment, or adaptive functioning can have different causes. Firstly, this may be a result of the distress experienced in IT-IEM, such as fear of metabolic crises or social problems associated with the diet (Weber et al., 2012). Secondly, neurological sequelae of IT-IEM can lead directly to cognitive or psychological problems and thus to worse psychological adjustment and adaptive functioning in everyday life (e.g. psychotic or depressive symptoms through CNS damage) (Walterfang et al., 2013). Thirdly, it is important to consider the interaction between HrQoL and psychological adjustment, since the literature shows impaired HrQoL in patients with mental disorders (Dey et al., 2012). Therefore, impaired HrQoL may be caused by mental health problems. In contrast, good HrQoL in IT-IEM patients may be explained by the theory of response shift (Sprangers & Schwartz, 1999). This would account for the often-seen improvement of HrQoL in chronically ill patients as a result of an accommodation process which involves changing internal standards, values and conceptualisation. According to Sprangers and Schwartz (Sprangers & Schwartz, 1999), a response shift results from the interaction of different variables: health status, mechanisms such as coping, and antecedents such as personality or sociodemographics.

Interestingly, HrQoL was more often reported to be impaired when rated by parents compared to self-ratings by patients. In line with this, a comparison of self- and proxy-ratings revealed better self-ratings in most domains (Packman et al., 2007). The fact that HrQoL of children with chronic health conditions is rated lower by parents than by the children themselves is well known from the literature (Upton et al., 2008). Furthermore, there is a close relation between the parent's rating of a child's HrQoL and the parent's own HrQoL (Eiser & Varni, 2013): Parents experiencing low HrQoL rate their child's HrQoL low as well. This

might be especially relevant in parents of children with IT-IEM, since these diseases demand intensive care and may have a great impact on the lives of caregivers (Hatzmann et al., 2009). Another explanation for the lower proxy-ratings may be the ability of parents to anticipate the future problems of the child. Young children in particular may not be aware of these to the same extent.

A major reason for the inconsistent findings may be attributed to methodological issues. Most of the HrQoL instruments were not specifically tailored to patients with IT-IEM. One study used an invalidated disease-specific instrument (Eminoglu et al., 2013). In addition, the HrQoL of IT-IEM patients was compared to different groups: population norms or other metabolic diseases. Sample sizes were often small, a state of affairs that is often found in paediatric research and especially in research in the field of rare diseases. Statistically, such small sample sizes make it more difficult to detect group differences. In addition, one study had a clear selection bias by only including patients who were cognitively able to answer questionnaires (Grünert et al., 2013). Another significant limitation is the choice of informants; most studies used proxy-reports which do not fully reflect self-reports of the patients. It is clear from the literature that these two kinds of reports are not interchangeable (Eiser & Varni, 2013).

Risk factors for HrQoL, psychological adjustment, and adaptive functioning

The second aim of this review was to detect risk factors for HrQoL, psychological adjustment, and adaptive functioning for IT-IEM patients. Only a few risk factors for psychological adjustment and adaptive functioning have been investigated so far, and none have been examined for HrQoL. The risk factors examined were mainly medical (Krivitzky et al., 2009; Mazariegos et al., 2012; Muelly et al., 2013). With regard to cognitive parameters, IQ was investigated in one study (Mazariegos et al., 2012). Two studies revealed that metabolic events in the neonatal period were associated with psychosocial adjustment: patients diagnosed as encephalopathic newborns had a higher risk of suffering from anxiety or depression during their lifetime than patients who were metabolically stable during the newborn period (Muelly et al., 2013). Adaptive functioning scores were lower for neonatal-onset than for late-onset patients (Krivitzky et al., 2009). Similar results have been found before and may be explained by the fact that crises have a negative impact on the developing brain, especially in highly vulnerable newborns (Landolt, Nuoffer, Steinmann, & Superti-Furga, 2002; Muelly et al., 2013).

Strengths and limitations of this review

This systematic review was conducted in accordance to the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) (Moher, Liberati, Tetzlaff, & Altman, 2009). In order to find as many eligible studies as possible, we applied several search strategies: we searched different databases and did not restrict the search to English articles. Additionally, we tried to find additional and / or unpublished studies by reference screening and contacting experts in the field. Study selection and data extraction were conducted independently by two reviewers, thereby diminishing the risk of bias. The main weakness of our review is the inability to pool results from the different studies. The different study designs and assessment methods did not permit such meta-analytic calculations. Nevertheless, better comparability of the results was attained by indicating effect sizes and their CI. Another limitation of this systematic review can be found in our comparison of studies with very different sample sizes (ranging from N = 4 to N = 92), the reason why the calculated effect sizes have to be interpreted carefully. Because the incidence rates of rare diseases are small and because there is only a very limited number of studies that could be included in our review, we decided not to exclude studies with small sample sizes (inclusion criterion N > 1). To account for this limitation, we considered sample sizes in the calculation of effect sizes by correcting mechanisms. The different sizes were also taken into account by computing CIs of effect sizes.

Suggestions for future research

Based on the findings of this review, several implications can be drawn. Firstly, HrQoL should be considered as an essential outcome parameter in future clinical trials. Up to now, treatment evaluations of patients with IT-IEM have predominantly focused on medical outcomes. However, because survival rates have increased considerably, improvement of HrQoL for patients with IT-IEM must be an additional major goal of new treatments.

Secondly, it is important to increase the methodological quality of psychosocial research among IT-IEM patients. Multicentre studies are necessary both to avoid convenience sampling with a high risk for biased data and to increase sample sizes. International patient registries (e.g. E-IMD, www.e-imd.com) can help to achieve this goal and to aggregate knowledge. This review has shown that a variety of assessment instruments is currently in use, thus complicating the pooling of results. Most of the studies used generic, non-disease-specific instruments. Only one of the reviewed studies used a disease-specific scale (Eminoglu et al., 2013); however, this was not validated. Generic instruments have the advantage that results can usually be compared to a healthy population or a population with

another disease (J. S. Cohen & Biesecker, 2010). However, they do not assess the specific problems of medical conditions. In contrast, disease-specific HrQoL scales are related to the distinct effects of a particular disease (Walterfang et al., 2013). They are more sensitive for special topics that are of interest and more meaningful for specific groups of patients. The use of disease-specific HrQoL assessment measures in clinical trials has been shown to be valuable in other severe medical conditions (Walterfang et al., 2013). To date, no validated, disease-specific measure is available for patients with IT-IEM. Furthermore, from a methodological viewpoint, it is desirable to consider different informants; because proxy-reports have several limitations, the patients' well-being should also be assessed using self-ratings.

Thirdly, knowledge of risk factors influencing HrQoL, psychological adjustment, and adaptive functioning is of great importance. Very few studies have addressed this topic at all, and where they did, research was restricted to medical or biochemical parameters or IQ. Medical parameters are weak predictors for HrQoL in most chronic diseases (Walterfang et al., 2013). In contrast, a systematic review exploring HrQoL in rare genetic conditions has emphasised that parameters explaining how patients coped with their disease were good predictors of HrQoL (Walterfang et al., 2013). As an example, the authors mentioned scales such as "acceptance of disability" or "sense of coherence", which were positive predictors for QoL, while feeling hopeless or having a fatalistic view correlated with lower QoL (Walterfang et al., 2013). Other predictors for HrQoL in chronic disease described in the literature include concepts such as locus of control, attachment, or well-being of the parents (Agostini et al., 2014; Dulfer et al., 2014; Fan, Eiser, Ho, & Lin, 2013). In IT-IEM patients, such individual and familial psychosocial risk factors have not yet been studied. Current research is, unfortunately, still focused on a fully biomedical model, instead of including the promising psychosocial perspective (Walterfang et al., 2013).

Clinical implications

The small number of studies, partially inconsistent results, and the few risk factors addressed make it difficult to draw implications for clinical practice. Since HrQoL, psychological adjustment, and adaptive functioning seem to be impaired in some patients, we suggest offering psychological support for patients and their families to help them cope more effectively with the disease. Knowing more about risk factors would allow the development of targeted interventions for certain groups of patients. Overall, we consider it important to support patients and their families with a comprehensive care model, including psychological and social interventions to complement the medical ones (De Ridder et al., 2008; Simons et al., 2006).

Conclusion

Research data on psychosocial factors in IT-IEM patients are generally sparse. However, the growing interest in the topic is underlined by the fact that seven of the 11 articles reviewed were published in 2012 or 2013. Further research and improved methodological quality of studies are required. Multicentre studies and the use of a standardised, disease-specific assessment tools are needed to establish HrQoL as an important additional outcome parameter in patient-centred research and clinical trials.

1.6. Authors' contributions

N.A.Z. carried out the search and selection of the articles, extracted the data and drafted the manuscript. M.H. participated in the selection process of the articles, was involved in the design of the study, and critically reviewed the manuscript. M.R.B. conceived of the study, was involved in the design of the study, and critically reviewed the manuscript. M.A.L. participated in the data extraction process, helped in drafting and revising the manuscript and coordinating the study. All authors read and approved the final version of the manuscript.

1.7. Acknowledgements

This systematic review was supported by radiz – Rare Disease Initiative Zurich, Clinical Research Priority Program for Rare Diseases, University of Zurich, Switzerland. We want to thank the following researchers who provided us with additional information about their published data (in alphabetical order): Marta Biernacka, Chiara Cazzorla, Gwendolyn Gramer, Sarah Grünert, Lauren Krivitzky, Wendy Packman, Annik Simons, and Diana Shellmer.

2. Living with intoxication-type inborn errors of metabolism – a qualitative analysis of interviews with paediatric patients and their parents

Reference: Zeltner N. A., Landolt M. A., Baumgartner M. R., Lageder, S., Quitmann, J., Sommer, R., Karall, D., Mühlhausen, C., Schlune, A., Scholl-Bürgi, S., Huemer, M. (2016). Living with intoxication-type inborn errors of metabolism - a qualitative analysis of interviews with paediatric patients and their parents. *Journal of Inherited Metabolic Disease Reports*, 1-9. doi: 10.1007/8904_2016_545

2.1. Abstract

Introduction: Progress in diagnosis and treatment of patients with intoxication-type inborn errors of metabolism (IT-IEM) such as urea cycle disorders, organic acidurias, or maple syrup urine disease is resulting in a growing number of long-term survivors. Consequently, health-related quality of life (HrQoL) of patients is increasingly regarded as a meaningful outcome parameter. To develop the first validated, disease-specific HrQoL questionnaire for IT-IEM, patients and parents were interviewed as content experts to identify major physical and psychosocial constraints and resources.

Methods: Focus group interviews with 19 paediatric IT-IEM patients and 26 parents were conducted in four metabolic centres in Austria, Germany, and Switzerland. Disease-specific HrQoL categories were established by qualitative content analysis

Results: Fourteen disease-specific topics related to the three well-established generic HrQoL dimensions of physical, mental, and social functioning were derived from the interview transcripts. Both patients and parents perceived dietary restrictions and social stigmatization as major burdens. Dietary restrictions and emotional burdens were more important for young (<8 years) patients, whereas cognition, fatigue and social issues were more relevant to older patients (≥8 years). Treatment-related topics had a significant effect on social and emotional HrQoL.

Discussion: By exploring patients' and parents' perspectives, 14 HrQoL categories were identified. These new categories will allow the development of a disease-specific, standardized questionnaire to assess HrQoL in paediatric IT-IEM patients. Age-appropriate information on the disease and psychosocial support targeted to patients' individual burdens are essential to the delivery of personalized care that takes account of physical, mental, and social dimensions of HrQoL.

1 sentence take-home message: Taking patients' and parents' perspectives into account allows the definition of meaningful follow-up parameters and the development of personalized interventions.

2.2. Introduction

Urea cycle disorders (UCD), organic acidurias (OA) and maple syrup urine disease (MSUD) are intoxication-type inborn errors of metabolism (IT-IEM) sharing main clinical and treatment characteristics. Patients must follow a low-protein diet, have to cope with the constant fear of life-threatening metabolic crises, and frequently develop neurocognitive impairments.

Considerable progress in recent decades in the diagnosis and treatment of IT-IEM has resulted in a growing number of long-term survivors (Batshaw et al., 2014; De Baulny et al., 2005). The long-term medical care and support of patients and families requires insight into subjective psychosocial conditions and health-related quality of life (HrQoL) (Bullinger, 2002). HrQoL is a multidimensional construct that represents "a patient's perception of the impact of disease and treatment on functioning in a variety of dimensions, including physical, psychological and social domains" (Varni et al. 1999, p. 126). As such, it is a meaningful outcome parameter for clinical trials and the evaluation of the quality and cost-effectiveness of treatment (Bullinger, 2002). Three general types of HrQoL assessment measures exist. Generic HrQoL instruments (e.g. the PedsQL (Varni et al., 1999)) compare HrQoL between healthy individuals and patients, chronic generic instruments (e.g. DISABKIDS (The DISABKIDS Group Europe, 2006)) serve to assess and compare HrQoL in patients with chronic diseases in general, and disease-specific instruments (e.g. the PKU-QOL (Regnault et al., 2015)) address the characteristics of a particular disease or disease group. The latter are therefore the method of choice in clinical trials (Walterfang et al., 2013). Since the concept of HrQoL is based on subjective experience, self-assessment using age-appropriate instruments is the gold standard (Matza et al., 2013). Self- and proxy-reports are not interchangeable (Upton et al., 2008); but proxy-reports are valuable in very young or cognitively impaired patients.

Although interest in psychosocial issues in IT-IEM has recently increased, research is still sparse and has methodological shortcomings (Zeltner et al., 2014). The first disease-specific assessment instrument for individuals with IT-IEM is currently under development by our research group. In this process, patients and parents are involved as "content experts" (Matza, Swensen, Flood, Secnik, & Leidy, 2004). Focus group interviews are the method of choice to identify topics, concerns and resources relevant in everyday life (Matza et al.,

2013). This paper presents the qualitative content analysis of focus group and single interviews with IT-IEM patients and their parents. The two main aims of this study were (1) to identify HrQoL topics relevant for paediatric IT-IEM patients and (2) to investigate differences in statement frequencies of topics related to the informant (patient or parent) and to the age of the affected child.

2.3. Methods

Subject recruitment

Physicians from four metabolic centres in Austria, Germany, and Switzerland invited IT-IEM patients (≤18 years) and their parents by phone or during routine consultations for participation. If patients were younger than 8 years or unable to participate due to neurocognitive impairment, only their parents were invited.

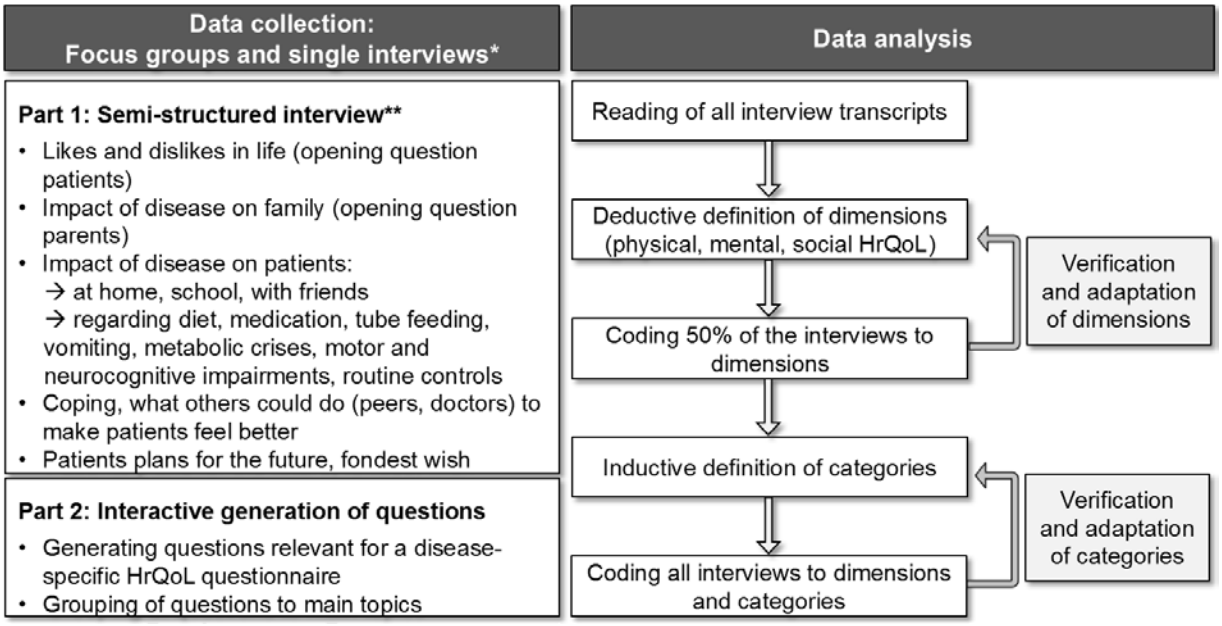
Focus groups and single interviews

Focus group interviews were conducted by a team of trained moderators with medical or psychological background in each centre. For patients and parents unable to attend, single interviews were arranged either in the hospital, by phone, or at home. Focus groups of 2-7 participants were composed based on patient's age (<8 years, 8-12 years, 13-18 years). Patients younger than 8 years were represented by their parents. Parallel patients' and parents' focus groups were conducted for 8-12 and 13-18 year olds. Each group was led by two trained moderators, who followed a manual specifically adapted for IT-IEM and based on the DISABKIDS methodology (The DISABKIDS Group Europe, 2006). Single interviews were conducted by one moderator following the manual. The focus group procedure is presented diagrammatically in Figure 6.

Data processing and analysis

Interviews were transcribed verbatim in German from audio recordings using transcription software (f4, 2014, Dr. Dresing & Pehl GmbH, Marburg, Germany). Statements used in the result section of this paper were translated to English by a professional interpreter. Two coders (N.A.Z., S.L.) analyzed the interviews according to the established qualitative data-analysis procedure developed by Mayring (Kuckartz, 2014; Mayring, 2010) using the MAXQDA software (MAXQDA, version 11, 1989-2015, VERBI Software – Consult – Sozialforschung GmbH, Berlin, Germany).

Statements identified in the transcripts were assigned to the three HrQoL core dimensions *physical*, *mental* and *social* HrQoL (World Health Organisation, 1948). Based on these core dimensions, categories were inductively defined. The system of categories was elaborated in several analytical cycles (Figure 7). Coding disagreements were resolved by discussion. Two psychologists not otherwise involved in the study assigned 42 randomly chosen statements to the 14 categories. Inter-rater reliability (J. Cohen, 1988) was "almost perfect" for one (Cohen's kappa = 0.94) and "substantial" for the second rater (Cohen's kappa = 0.79) (Landis & Koch, 1977).



*Part 2 was omitted in single telephone interviews.
**Discussion among participants was encouraged during the interview. Change in order of the topics was thereby tolerated. Moderators made sure that all topics were addressed.

Figure 7: Content of interviews

Based on the developed manual and content analysis based on Mayring an Kuckartz (Kuckartz, 2014; Mayring, 2010)

Educational status of parents was assessed using the ISCED Manual (OECD, 1999) which differentiates seven internationally comparable levels. Sex distribution among age groups was examined by fisher's exact tests. Chi square tests and standardized residuals were used to detect differences of statement frequencies per category between informant groups (patients / parents) and patients' age groups. Issues mentioned repeatedly by single participants resulted in multiple coded statements; length of statements was not considered. Stepwise comparisons were calculated between core dimensions, grouped categories and single categories (see Table 6). Analyses were performed using the statistical software package

SPSS, version 20.0 for Windows (SPSS Inc., Chicago, IL, USA). Statistical significance was defined as $p < 0.05$.

2.4. Results

Sample characteristics

Thirty (71%) of 42 invited families participated, resulting in a study sample of 19 children and adolescents (n = 9 females, n = 10 males; n = 9 OA, n = 9 UCD, n = 1 MSUD; age range 9.5 to 16.5 years, mean = 13.0 ± 2.3 years) and 26 parents (n = 25 mothers, n = 1 father). All parents had at least one child affected by IT-IEM (n = 12 females, n = 16 males (from which n = 2 siblings); n = 18 OA, n = 8 UCD; patients' age range 0.9 to 16.8 years, mean = 10.3 ± 4.7 years) (see Table 5). Educational status of parents (mean of fathers and mothers educational status) was mean = 3.64 (± 1.12, range 2-6). Distribution of patients' sex among age groups did not significantly differ for patients ($p = 0.18$) or parents ($p = 0.09$).

Categorical system

A total of 915 statements addressing patients' HrQoL were identified from 19 transcripts of 5 patient and 6 parent focus groups and 5 patient and 3 parent single interviews. Fourteen content categories were defined and allocated to one of the core dimensions (physical, mental and social HrQoL) (Table 6). Frequencies of statements per category for patients and parents are shown in Figure 8.

Physical dimension of HrQoL

Symptoms and treatment of the disease relate to the physical dimension of HrQoL. *Dietary restrictions* (intake of regular food and special low-protein food) were a main topic for both patients and parents (Figure 8). However, attitudes varied widely from "being used to dietary restrictions" or even having an "aversion to proteins" to complaints about "missing forbidden food and freedom of food choice" and "required organisational effort". The latter were especially encountered in social situations such as barbecues or school camps. A 16-year-old girl commented: "When I go to school camp, I have to take a second suitcase along. It's all food. And a woman cooks especially for me".

Table 5: Number of interview participants in focus groups and single interviews

	Patient's age			
	<8 years	8-12 years	13-18 years	**All age groups**
N patients	-	9	10	**19**
N parents	9	9	8	**26**
N patients in focus group interviews	-	6	8	**14**
N patients in single interviews	-	3	2	**5**
N parents in focus group interviews	8	8	7	**23**
N parents in single interviews	1	1	1	**3**
Total participants	**9**	**18**	**18**	**45**

According to parents, pre-schoolers did not experience diet as particularly burdensome. In contrast, parents experienced caring for a young child's diet as most difficult and stressful. They felt disburdened when their child was able to take over responsibility by self-monitoring or indicating need for their sick-day regimen. The mother of a 5-year-old girl stated: "When she was two or three years old, she would often snatch a piece of sausage and put it into her mouth (…). By now I know that she won't do this anymore, that's something I can rely on". However, diet places an incessant strain on family life. Parents felt children used food intake or vomiting to exert pressure or gain attention, as explained by the mother of a 16-year-old: "That's always some form of pressure of hers, although she often isn't able to express herself that well; but with food she's totally in control of me and that she knows very well". Against this background, parents considered tube feeding supportive, since arguing about food intake became less central: "As soon as he had received the PEG, we were happy. We were no longer at the hospital, the pressure on me was gone, I was no longer under pressure" (Mother of a 13-year-old). In contrast, patients may hide their tube: "Absolutely nobody is allowed to see it [the tube] (…) and nobody is allowed to know about it, except close relatives and friends" (Mother of a 10-year-old).

Although intake of dietetics and medication was daily routine, the unpleasant taste of amino-acid mixtures remained a major issue and patients preferred pills over drinks whenever possible. Moreover, the lack of flexibility allowed by a tightly scheduled intake of medication and supplement interfered with everyday life and spontaneous engagement in social

situations. Side-effects such as diarrhoea or body odour, namely the fishy odour of carnitine, were additional constraints in social situations.

The majority of patients felt blood sampling (category *routine controls / hospital*) to be extremely stressful and commented more frequently on this subject than parents (not statistically significant). Adolescents coped better with blood sampling but complained that hospital appointments reduced their leisure time.

Motor deficits and limitations in keeping up with peers were the most burdensome limitations for children with IT-IEM. One of the fondest wishes expressed by non-ambulatory children young than 8 years was "being able to walk and run like others". *Fatigue / nausea / vomiting* were especially important for older patients comparing their performance with healthy peers'. „Because when I overdo it, I have to throw up. I simply don't manage as much as all the others" (16-year-old male patient working as apprentice).

Metabolic crises were traumatizing experiences and caused constant fear of potential new crises, infections and other triggers. Most patients had experienced metabolic crises during infancy, and it was mainly their parents who remembered the details, as the father of a 7-year-old stated: "We had five crises with him, ended up five times in intensive care. Once we were abroad and the physicians said: You know, we can't do anything, the boy will die". The mother of a 16-year-old said: "Gastro-intestinal flu: all alarm bells ring, (…) this is a one-way ticket to hospital". Parents and patients reported always planning their annual leave in proximity to metabolic hospitals they trust to avoid encountering medical staff unfamiliar with the disease.

Comparing frequencies of statements

The frequency distribution of patients' and parents' statements significantly differed among the categories associated with treatment (χ^2 (3) = 25.24, $p < 0.05$). Patients mentioned *tube feeding* significantly less frequently than parents.

Comparison of patients' reports revealed a significant age difference between symptom and treatment statements (χ^2 (2) = 11.44, $p < 0.05$). Eight- to 12-year-old patients made more statements about treatment, while 13-18 year olds talked more frequently about symptoms and limitations. Comparing categories describing symptoms revealed that, in contrast to parents of older children, parents of patients younger than 8 years made no statements related to *fatigue / nausea / vomiting* (χ^2 (4)= 15.18, $p < 0.05$). In the categories describing treatment, parents of younger children talked more frequently about *dietary restrictions* and less frequently about *medication / dietetics* than parents of older children and adolescents (χ^2 (6) = 22.19, $p < 0.05$).

All other comparisons in the physical dimension between different age and respondent groups were not significant.

Table 6: System of disease-specific HrQoL categories based on the content of the interviews

Dimension	Category	Group	Description of category
Physical	**Metabolic crises / anticipation of crises**	Symptoms	Experiencing metabolic crises, anticipation of crises (i.e. infections, hygiene), emergency admissions because of crisis
	Physical limitations	Symptoms	Motor limitations, organ problems
	Fatigue / nausea / vomiting	Symptoms	Fatigue, nausea and vomiting (events not immediately connected to metabolic crisis and emergency admissions)
	Dietary restrictions	Treatment	Dietary restrictions, regular food intake, low-protein food
	Medication / dietetics	Treatment	Drug and dietetics intake, side effects
	Tube feeding	Treatment	PEG tube, nasogastric tube
	Routine controls / hospital	Treatment	Routine controls in the hospital / by the physician, reactions to blood sampling
Mental	**Negative emotions**	Emotions	Statements with negative emotional content. Sadness, anger, crying, feeling different than friends, shame (not wanting to make the condition public), wanting the disease gone
	Positive emotions	Emotions	Statements with positive emotional content. Being happy, satisfied, feeling good and "normal" with the condition
	Cognitive functioning		Cognitive functioning, especially in school, disturbed concentration, mental disability
	Independent living		Feeling restricted in conduct of life, choice of employment, planning of leisure time
Social	**Friends**	Social life, social support	Having friends, social support / social inclusion by friends
	Family	Social life, social support	Statements concerning the family (parents, siblings, grandparents, uncles, aunts…) and their handling of the condition
	Stigmatization / exclusion		Being treated differently (negative / positive) by peers and society based on the condition: teasing, interrogation regarding condition, being pitied, exclusion (i.e. difficulties finding a school, going on school excursions)

Mental dimension of HrQoL

The mental dimension encompasses statements related to emotions, cognition and issues of independent living. *Negative emotions* were predominantly reported. The most frequent "fondest wish" of the patients was "not to have the disease" or to be "more like normal kids". The perception of not being able "to do what other kids do" caused frustration. The impression of being "different" in some cases led to feelings of shame, making patients averse to others being informed about their condition. Since having a meal together is of high social significance, IT-IEM patients often felt socially excluded. The mother of a 7-year-old reported: „The kids [at Kindergarten] were not allowed to share [food] with him. This troubled him a lot, the fact that he now suddenly did not belong to the group. He cried bitterly then".

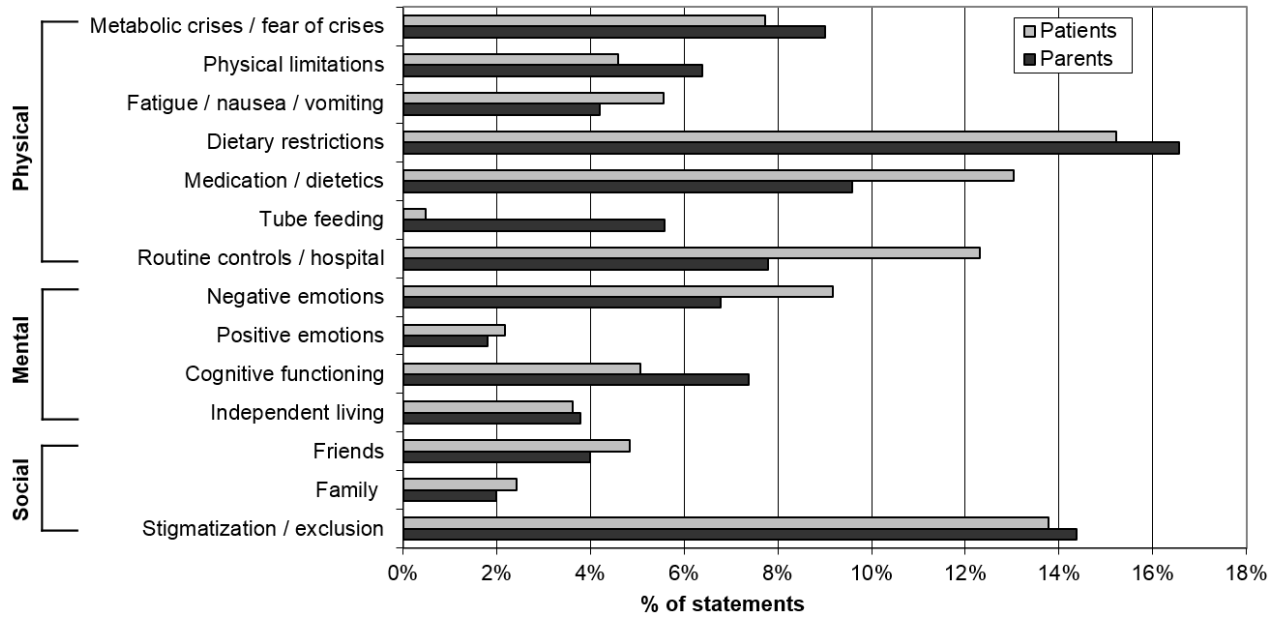


Figure 8: Percentage of statements from total statements per category, for each patient and parent interviews (both for patients aged from 8 to 18 years)

Cognitive functioning and school performance gained increasing significance for older children and adolescents. Children attending regular schools felt inferior when comparing their school performance with those of their healthy peers. Parents of children with severe cognitive impairment attending special schools worried about their children's performance but had the impression that the children themselves did not.

Comparing frequencies of statements

Parents' statements regarding *emotions*, *cognitive functioning* and *independent living* significantly differed between age groups (χ^2 (2) = 29.70, $p < 0.05$). In the younger age groups more statements addressed *emotions*, while *cognitive functioning* was more important to the 13-18 years group.

All other comparisons in the mental dimension were not significant.

Social dimensions of HrQoL

The social dimension refers to the impact of the disease on social life and stigmatization experiences. Patients and parents generally felt supported by family and close friends. The second highest number of statements was attributed to the *social stigmatization / exclusion* category (Figure 8).

Peers teased patients because of physical or cognitive limitations or side effects of medication. A 9-year-old boy reported: „Actually, my disease is okay, except that some kids make fun of it (…). The medication smells of fish, so they call me fishhead and say that I stink of fish".

Patients of all age groups considered it difficult to explain their condition in a comprehensible way. "Well, my problem is simply that they keep asking: Why do you have that thing? And I don't know exactly what I'm supposed to answer" (10-year-old patient). Because of her strict diet, a 16-year-old girl was referred to as "the pickiest person we know" by her schoolmates. "I try to explain to them what it is about. But some of them just don't want to understand". Like their children, parents considered it almost impossible to explain the complex, rare disease to others in an understandable way. They felt frustrated because they perceived that their environment had no understanding of their child's condition. Criticism of or interference with parenting style (e.g. comments that mothers were "too strict" about diet or offers of inappropriate meals) were experienced as stressful. Attempts to avoid social exclusion, for instance from school camps, exerted intense stress on families (escorting the child; precooking meals). Finding a sensitive social environment was considered of the utmost importance.

Comparing frequencies of statements

Compared to 8-12 year-old patients, 13-18 year-old patients commented less on *social life, social support* (χ^2 (1) = 11.53, $p < 0.05$).

All other comparisons in the social dimension were not significant.

2.5. Discussion

This study explored how IT-IEM affects daily life and identified 14 categories relevant for patients' HrQoL. The evolving categories could coherently be allocated to the core dimensions of *physical*, *mental*, and *social* HrQoL, resulting in a structure consistent with well-established generic and chronic disease HrQoL questionnaires (The DISABKIDS Group Europe, 2006; The KIDSCREEN Group Europe, 2006; Varni et al., 1999). Categories within the *social* and *emotional* dimensions are similar to other questionnaires (The KIDSCREEN Group Europe, 2006; Vogels et al., 1999), while categories within the *physical* dimension mostly reflect disease-specific issues. Notably, other questionnaires refer to more than three dimensions (e.g. Varni et al. 1999), while this study kept to the three core dimensions represented in almost all HrQoL questionnaires (Rajmil et al., 2004).

It is an important strength of this study that the individual perspectives of patients were considered and that the proxy-reports from parents allowed insight into perspectives of young and / or cognitively impaired patients. Despite international cooperation, owing to the rarity of the diseases, the sample size is limited and patient recruitment was not free of selection bias.

Analyses of group differences demonstrated that the importance of specific HrQoL-related topics varied depending on patients' age and between parents and patients. Diet and emotional contents were predominant when patients were young (<8 years), and both patients and parents had to build up knowledge and routine concerning food choice and preparation and intake of medication and dietetics. Furthermore, hospital stays were emotionally burdensome for young children, and families had to deal with uncertainty related to disease progression, neurocognitive development, and upcoming metabolic crises. Dealing with diet and uncertainty have been reported to be mayor burdens for parents with children with metabolic diseases before (Cederbaum et al., 2001; Pelentsov, Laws, & Esterman, 2015). As coping strategies significantly influence HrQoL in different chronic diseases (Graven & Grant, 2013), tailored support may be helpful. Our results suggest that families with young children in particular would benefit from support targeting these uncertainties and coping with diagnosis and treatment. In addition, immediately at diagnosis patients should be informed about support groups, which have been shown to be important informational resources in rare disorders (Hall, 2013; Khangura et al., 2015). Accordingly, the majority of participants in this study greatly appreciated the exchange with others in the context of the interviews and expressed their wish to have this opportunity more frequently. Unfortunately, research shows

that few families with children with rare diseases receive psychosocial support at time of diagnosis (Anderson et al 2013).

In this study, cognitive functioning and feeling fatigued or less productive gained significance for school-aged and adolescent patients, along with the increasing importance of school performance and social comparison with peers. Importantly, adolescents reported less frequently about social support than younger patients but still encountered experiences of stigmatization, resulting in an imbalance of constraints and resources. Our results thereby suggest that transitional phases (to school, to adolescence), often combined with social and physical challenges, deserve special attention, as this has been reported before for other inborn errors of metabolism (Khangura et al., 2015; Packman et al., 2012). Sharing meals with others is known to have high social significance, hence patients living with dietary restrictions experience numerous potentially stigmatizing situations (Diesen, Wiig, Grut, & Kase, 2014). Since perceived stigmatization is a predictor for poorer psychological adjustment (Masnari et al., 2013), it is of great importance that patients are supported in so called stigma-handling strategies (Diesen et al., 2014), such as social skills training or school-based interventions, in which peers are provided with basic information about the condition, resulting in better understanding (Sharman, Mulgrew, & Katsikitis, 2013).

In contrast to parents, patients talked reluctantly about tube feeding. Content of statements indicates tube feeding meant considerable relief for parents in terms of reduced worries and struggles with children about food intake. Consistent with this, previous research showed that tube feeding has a positive impact on parental HrQoL (Fabre et al., 2013). In contrast, feelings of shame and embarrassment seemed to be a reason why patients did not want to talk about their tube in the focus groups – which goes along with the psychosocial impact of tube feeding mentioned in the literature (Burmucic, Trabi, Deutschmann, Scheer, & Dunitz-Scheer, 2006). We are aware of the limitation that the perspectives of very young and / or severely compromised patients on this issue have not been included in this study.

Based on the results of the focus groups, two main clinical implications can be drawn. Firstly, patients with IT-IEM and their parents have significant need for comprehensible explanations and information concerning their disease. Both patients and parents reported difficulties in making the condition understandable to the social environment. For other diseases (e.g. diabetes type 1), this need has been met by age-appropriate, verbal information from medical professionals and attractive paper- or IT-based materials (Årsand et al., 2012; Murphy, Wadham, Rayman, & Skinner, 2007). Improved understanding of the disease may motivate patients to reach better compliance (Sharman et al., 2013). Being able to explain the disease may help patients and parents to cope better with stigmatizing social situations such

as the often-experienced exclusion from school or leisure activities. In addition, low-threshold access to information about IT-IEM (e.g. informative homepages, guidelines) and metabolic expert advice would help physicians who are not specialized in the metabolic field in their communication with families.

Secondly, beyond essential medical treatment, psychosocial care should be offered to IT-IEM patients and parents. It has been shown that a child's wellbeing is considerably influenced by family variables (Landolt, Grubenmann, & Meuli, 2002), and although the interviews in this study focused on the wellbeing of patients, parents spontaneously reported high levels of distress, which require appropriate support.

Remarkably, of the 26 participating parents only one was male. This highly unequal gender distribution narrows the breadth of the parent perspective but seems to reflect real-life patterns. In many families, it is still mothers who are the primary health carer. In their traditional role as major income earner of the family, fathers are less present in the hospital setting and take other functional roles in caring for the child, such as seeking information (Yeh, 2004). The underrepresentation of fathers in research focusing on children with chronic diseases is a common fact that it is important to note (Goldstein, Akre, Belanger, & Suris, 2013).

Studies in other diseases clearly revealed that physicians underestimate the impact of disease and treatment on emotional and social domains (Srikrishna, Robinson, Cardozo, & Gonzalez, 2009). Treatment issues were a main concern for patients in this study because they hampered everyday life and made the disease perceivable for others. Thus, the fondest wishes of the patients to "be normal" and "not have the disease" should motivate physicians and dieticians to consider even more highly that the most feasible and practical treatment protocol serves patients and families best. Side effects of medication, such as an unpleasant smell, diarrhoea and frequent intake of disliked amino-acid mixtures, may impair emotional and social well-being more than expected. Additionally, fear of blood sampling made hospital appointments extremely stressful for many patients. It is well established that, besides local anaesthetics, psychological techniques (e.g. relaxation techniques, developmentally appropriate distraction) are highly effective in reducing pain and anticipatory fear (Duff, 2003). It has been shown in other chronic paediatric diseases that addressing social issues and emotional distress during regular hospital follow-ups is supportive and that the use of HrQoL questionnaires (Santana & Feeny, 2013) significantly increases meaningful patient-physician communication and patient wellbeing (Velikova et al., 2004).

Conclusion

The categories identified describe HrQoL of IT-IEM patients and will allow the construction of a disease-specific HrQoL questionnaire. Care for IT-IEM patients can be improved by providing appropriate information about the disease and individualized psychosocial support to ameliorate the multifaceted effects of the disease on physical, mental and social wellbeing.

2.6. Authors' contributions

N.A.Z. was involved in designing the study, collected and analyzed the data, and drafted the manuscript. M.A.L. was involved in designing the study, gave advice on data collection and analysis, and critically reviewed the manuscript. M.R.B. was involved in designing the study, contributed patient data, and critically reviewed the manuscript. S.L. assisted in collecting and analysing the data. J.Q. was involved in designing the study. R.S. was involved in designing the study and collecting the data. C.M., A.S., D.K., and S.S. contributed patient data. M.H. provided the original concept of the study, coordinated the study, and revised the manuscript. All authors read and approved the final version of the manuscript.

2.7. Acknowledgements

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3. Development and psychometric evaluation of the MetabQoL 1.0 – a quality of life questionnaire for paediatric patients with intoxication-type inborn errors of metabolism

Reference: Zeltner, N. A., Baumgartner, M. R., Bondarenko, A., Ensenauer, R., Karall, D., Kölker, S., Mühlhausen, C., Scholl-Bürgi, S., Thimm, E., Quitmann, J., Burgard, P., Landolt., M. A., Huemer, M. (in press). Development and psychometric evaluation of the MetabQoL 1.0 – a quality of life questionnaire for paediatric patients with intoxication-type inborn errors of metabolism. *Journal of Inherited Metabolic Disease Reports.* doi: 10.1007/8904_2017_11

3.1. Abstract

Introduction: This study is part of the "European network and registry for intoxication type metabolic diseases" (E-IMD) project. Intoxication-type inborn errors of metabolism (IT-IEM) such as urea cycle disorders (UCD) and organic acidurias (OA) have a major impact on patients' lives. Patients have to adhere to strict diet and medication, and may suffer from metabolic crises and neurocognitive impairment. Disease-specific health-related quality of life (HrQoL) assessment questionnaires are the method of choice to estimate the subjective burden of a disease. To date, no such instrument is available for IT-IEM.

Methods: Disease-specific patient- and parent-reported HrQoL questions were constructed in German based on focus group interviews with patients and parents. Questionnaires for patients from 8-18 years were piloted with 14 participants (n = 9 children and adolescents, n = 5 parents) by cognitive debriefing and tested psychometrically with 80 participants (n = 38 patients, n = 42 parents) for item characteristics, validity, and reliability to construct the first version of a disease-specific HrQoL questionnaire.

Results: Twenty-eight questions were selected based on item descriptives. Scales of self- and proxy questionnaires demonstrated acceptable to excellent reliability in terms of internal consistency (Cronbach's $\alpha = 0.70$ to 0.93). Scales and total scores correlated with those of generic HrQoL questionnaires, showing convergent validity.

Discussion: The MetabQoL 1.0 questionnaire exhibits sound psychometric properties and is a promising step towards assessing patient-reported outcomes in research and clinical practice. It provides a solid basis for translation into other languages and further elaboration and psychometric exploration in larger populations.

One sentence take-home message: A newly developed disease-specific health-related quality of life questionnaire for intoxication-type inborn errors of metabolism (MetabQoL 1.0) allows insight into the subjective burden of disease among children and adolescents.

3.2. Introduction

This study is part of the "European network and registry for intoxication type metabolic diseases" (E-IMD) project, focusing on intoxication-type inborn errors of metabolism (IT-IEM) such as urea cycle disorders (UCD) and organic acidurias (OA). Estimated incidences are 1:35'000 for UCD (M. L. Summar et al., 2014) and 1:21'000 for OA (Dionisi-Vici et al., 2002). Recently, the natural course of the diseases has been described in two large samples (Kölker, Garcia-Cazorla, et al., 2015; Kölker, Valayannopoulos, et al., 2015; Waisbren, Gropman, & Batshaw, 2016). These reports highlight that IT-IEM have a major impact on patients' lives: Strict diet, daily intake of medication, the permanent risk of severe metabolic crises, and neurological sequelae are only some of the issues that the growing number of long-term surviving patients and their families face. Therefore, it is of utmost importance to consider health-related quality of life (HrQoL) as a major outcome parameter for this patient group besides medical and biochemical measures (Matza et al., 2004).

HrQoL is defined as "a patient's perception of the impact of disease and treatment on functioning in a variety of dimensions, including physical, psychological and social domains" (Varni et al. 1999, p.126). Due to the subjectivity of this construct, self-assessments by patients are the preferred data source (Matza et al., 2013). However, although self- and proxy assessments e.g. by parents often differ, parents can be very valuable as an additional source of information, especially in young or severely affected patients (Upton et al., 2008).

There are three main types of HrQoL assessment tools. Generic tools such as the PedsQL (Varni et al., 1999) target the general population and allow comparison between healthy individuals and individuals affected by any kind of disease. Chronic-generic tools such as the DISABKIDS (The DISABKIDS Group Europe, 2006) allow more specific comparison between individuals affected by different diseases. Disease-specific tools such as the PKU-QOL (Regnault et al., 2015) investigate the impact of a particular disease or disease group on patients' life. They have shown high responsiveness to change of HrQoL (S. Wiebe et al., 2003) and are therefore the method of choice for measuring this outcome parameter in clinical trials or long-term patient management.

No such disease-specific instrument was available for IT-IEM (Zeltner et al. 2014). We therefore developed a questionnaire of this type, the MetabQoL 1.0, following the ISPOR Guidelines (Matza et al., 2013). Four versions were constructed: self- and parent reporting

versions for patients from 8-18 years and self- and parent reporting versions for patients younger than 8 years. The development process encompassed three main steps. First, focus group interviews were performed to identify core topics with high content validity; details of the procedure and results have been reported elsewhere (Zeltner et al., 2016). Items were constructed based on focus group results and the available literature (e.g. The DISABKIDS Group Europe 2006; Regnault et al. 2015).

This paper describes the second and third steps of the questionnaire's development for the patients' group aged from 8 to18 years. The second step was the exploration and adaptation of item comprehensibility and clarity ("cognitive debriefing") in children, adolescents, and adults. The third step was the psychometric evaluation of the instrument in a larger group. Item descriptives (e.g. mean, missing values, selectivity) served to select the most useful items, internal consistency of the questionnaire was calculated to assess reliability, and correlations between scores of the new instrument and those of well-established generic HrQoL questionnaires were used to test for convergent validity.

3.3. Methods

Subject recruitment

For the cognitive debriefing, healthy children and adolescents as well as paediatric patients with UCD, OAs, or maple syrup urine disease (MSUD) from 8 to18 years were recruited in Innsbruck and Zurich to test the comprehensibility and feasibility of the questionnaire booklet. Patients who had received a liver transplant for treatment of their metabolic disease were asked to recall the period before transplantation.

For psychometric evaluation, a sample of families with at least one child diagnosed with UCD or OA aged 8-18 years from the metabolic centres of Düsseldorf, Hamburg, Heidelberg, Innsbruck, and Zurich was invited by a member of the local medical team to participate in the study. Transplanted patients were not included.

For both study phases (cognitive debriefing and psychometric evaluation), individuals were excluded if they had insufficient command of the German language or were incapable of answering the questions due to neurocognitive constraints.

Materials

Questionnaire booklets were created for patients and parents. Patient self-report questionnaire booklets and parent proxy-report questionnaire booklets both contained basic demographic items, the newly developed questions for the MetabQoL 1.0 instrument, and well-established HrQoL questionnaires (described below). Parents worked on the booklet independently, while patients answered all questions in a one-to-one interview with a trained interviewer with medical or psychological background at their homes or at the hospital.

MetabQoL 1.0

Patient and parent questionnaires included the set of newly developed items for the MetabQoL 1.0 instrument. The items were elaborated by discussion among four of the authors (N.A.Z., M.L., M.B., M.H.); they were originally written in German and were translated into English for presentation in this report.

A set of 52 questions was developed for parallel self- and proxy assessment for patients from 8 to 18 years. Fifty questions are answered using 5-point Likert frequency scales (options: never, seldom, sometimes, often, always), with an additional answer option (e.g. “no problem with this”) for questions not applicable for all patients (e.g. tube feeding). Two questions assess disease severity during the last 12 months: 1) disease has been “not bad at all”, “slightly bad”, “medium bad”, “bad”, “very bad” and 2) number of hospital admissions “never”, “once”, “twice”, “3 to 5 times”, “6 times or more”. Item scores can be aggregated to scale scores, which represent the core dimensions of physical, mental, and social HrQoL and a HrQoL total score.

PedsQL and DISABKIDS

Patients’ generic and chronic-generic HrQoL was assessed using self- and proxy assessment versions of the PedsQL (Felder-Puig et al., 2004; Varni et al., 1999) and the DISABKIDS-37 (The DISABKIDS Group Europe, 2006); both instruments are reliable in terms of psychometric properties.

The PedsQL is a well-established instrument to assess the generic HrQoL of children and adolescents from 8 to18 years with a recall period of four weeks. Twenty-three items are answered on a 5-point Likert frequency scale. The PedsQL has scale scores for physical, social, emotional, and school-related HrQoL. Social, emotional, and school-related HrQoL can be aggregated to a psychosocial health score. Sum scores of all scales represent the

HrQoL total score (Varni et al., 1999). The internal consistency of the PedsQL total scale scores in the current sample was good to excellent, with Cronbach's α = 0.88 / 0.93 (self-/proxy report).

The DISABKIDS assesses HrQoL in children with chronic disease from 8 to 16 years with a recall period of 4 weeks. The answering format comprises 5-point Likert frequency scales. Six scales represent the three main dimensions of HrQoL: limitation and medication (physical HrQoL), independence and emotion (mental HrQoL), and inclusion and exclusion (social HrQoL). Furthermore, a total HrQoL score can be computed including all scales (The DISABKIDS Group Europe, 2006). The internal consistency of the DISABKIDS total scale scores in the current sample was good to excellent, with Cronbach's α = 0.87 / 0.95 (DISABKIDS self-/proxy report).

Cognitive debriefing

The MetabQoL 1.0 questionnaire was tested for comprehensibility, relevance, and feasibility in a sample of five patients (n = 2 female, n = 3 male; age range = 8.72-16.77 years, mean = 12.42 ± 4.05 years; n = 1 liver transplanted) and their parents (n = 5 mothers). After completing the questionnaire one-to-one interviews were conducted at the patient's home, at the hospital or by phone. Feasibility of the whole booklet for psychometric evaluation containing all three HrQoL questionnaires (MetabQoL 1.0, PedsQL, DISABKIDS) was assessed by interviewing four healthy participants (n = 2 female, n = 2 male; age range = 9.83-18.09 years, mean = 12.66 ± 4.36 years) at home. All comments were discussed, and two of the authors (N.A.Z., M.H.) decided adaptations to the booklet.

Psychometric evaluation

Cases were excluded if ≥ 20% of the MetabQoL 1.0 data were missing. The randomness of the remaining missing data was analysed with Little's MCAR test to ensure that the imputation method was appropriate. Missing values in the MetabQoL 1.0 were then imputed using the full information maximum likelihood (FIML) method (Arbuckle, 1996).

The PedsQL and the DISABKIDS were scored according to the corresponding manuals (The DISABKIDS Group Europe, 2006; Varni et al., 1999). Original scores of the MetabQoL 1.0 (never / not applicable = 0, seldom = 1, sometimes = 2, often = 3, always = 4) were rescaled to values between 0 and 100 (0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0). Values of positively formulated items were reversed to allow comparability with PedsQL and DISABKIDS. Accordingly, best HrQoL was indicated by values of 100, worst by 0. Scales

of physical, mental, and social HrQoL were computed by the mean of the corresponding item values. A total score was computed by the mean of all item values of the physical, mental, and social scales.

Item selection was performed in two steps. The first step was based on cut-offs derived from the literature (Bühner, 2011) and the distribution of item descriptives in the current sample. Items were considered for exclusion if their mean value was ≥ 90 / 85 (self-/proxy report), or if selectivity was < 0.3, or if correlation with other items was ≥ 0.80, or missing raw data was > 5% (indicating e.g. low acceptance of an item), or if lack of comprehensibility had been documented in the interview setting.

The second selection step consisted of screening these problematic items. Items remained in the instrument if their content was vital to cover main issues from the focus groups, or in the interest of parallel content and comparability of the self- and proxy report questionnaires.

Reliability defined as internal consistency for total and scale scores was determined using Cronbach's alpha. Scores ≥0.7 were considered acceptable (Scientific Advisory Committee of the Medical Outcomes Trust, 2002). Concurrent validity between MetabQoL 1.0 and PedsQL/DISABKIDS subscales and total scores was determined by Spearman correlations. Due to the small sample size, factor analysis models were not applicable (Bühner, 2011).

Analyses were performed with the statistical software package SPSS, version 22.0 and Amos Version 23.0 for Windows (IBM Corp. IBM SPSS Statistics for Windows. Armonk, NY: IBM Corp). A predefined significance level of $p < 0.05$ was set for all tests.

3.4. Results

Sample characteristics

Of 87 families approached, 46 (53%) participated in the psychometric evaluation. This resulted in a sample of 80 participants; 38 patients (n = 17 female, n = 21 male; age range = 7.86 – 17.77 years, mean age = 12.56 ± 3.03 years; n = 25 OA, n = 13 UCD) with IT-IEM and 42 parents (n = 35 mothers, n = 7 fathers) of children with IT-IEM (n = 19 female, n = 23 male; age range = 8.49 – 18.34 years, mean age = 13.42 ± 3.04 years; n = 27 OA, n = 15 UCD; 32 parent-child pairs).

Cognitive debriefing results

Overall, patients and parents reported good feasibility of the MetabQoL 1.0 and the validation booklet. The majority of the questions were considered comprehensive and relevant by patients and parents. The guidance of the interviewer was important to improve patients' concentration and ensure that they understood the questions. Some questions (addressing e.g. motoric function, tube feeding) were not applicable for all patients, but their parents were aware of their relevance for other patients. Five questions had to be rephrased to increase comprehensibility and one to increase relevance.

Psychometric evaluation results

The self- and proxy questionnaires showed 6.01% / 1.31% of randomly missing data in the MetabQoL 1.0 (Little's MCAR-test, $x^2 = 10.02$ / $x^2 = 464.94$, DF = 292 / DF = 492, p = 1.00 / p = 0.80), and therefore qualified for the application of data imputation.

Item selection

The item selection process resulted in a final sample of 28 items. Selected items and their scale affiliation, representing the first version of the MetabQoL 1.0, are listed in Table 1. Detailed item descriptives and the selection process of all items are shown in supplementary Table S1.

Table 7: Items included in the first version of the MetabQoL 1.0 for self-assessment

	Items*[1] included based on item analysis*[2]	**Scale**
1	Does it bother you that you are not allowed to eat anything you want?	Physical
2	Does it bother you that you have to eat even when you are not hungry?	Physical
3	Does it bother you that you have to take medications?	Physical
4	Does the taste of your medications bother you?	Physical
5	Does it bother you that you have regular check-ups?	Physical
6	Are you afraid of having blood taken?	Physical
7	Does it bother you that you may have to go to the hospital due to an emergency?	Physical
8	Do you worry about your blood test results?	Physical
9	Does your metabolic disorder bother you when you are playing or during other activities?	Physical

10	Does it bother you that you cannot move as well as others?	Physical
11	Does it bother you that you get tired quickly?	Physical
12	Does it bother you that you often feel sick to your stomach?	Physical
13	Does it bother you that you have a feeding tube?	Physical
14	Do you have trouble keeping up in school / in your apprenticeship because of your metabolic disorder?	Mental
15	Do you feel alright?	Mental
16	Are you worried about your metabolic disorder?	Mental
17	Are you sad because you have a metabolic disorder?	Mental
18	Are you angry at having a metabolic disorder?	Mental
19	Are you afraid of the future because of your metabolic disorder?	Mental
20	Are you having problems doing things with friends because of your metabolic disorder?	Social
21	Are others less willing to be friends with you because of your metabolic disorder?	Social
22	Does it bother you that your parents or others in your family are particularly worried about you because of the metabolic disorder?	Social
23	Does it bother you that people treat you differently because of your metabolic disorder?	Social
24	Does it bother you that many people do not understand your metabolic disorder?	Social
25	Do you get left out because of your metabolic disorder?	Social
26	Does it bother you when other people feel sorry for you?	Social
27	How bad were your problems with your metabolic disorder over the last 12 months?	Severity
28	In the past 12 months, how often did you have to be admitted to the hospital in an emergency?	Severity

*[1] The proxy-assessment questionnaire consists of parallel rephrased items (e.g. item 1: Does it bother your child that he/she is not allowed to eat anything he/she wants?)
*[2] Answering options: never, seldom, sometimes, often, always (items 1-26); not bad at all, slightly bad, medium bad, bad, very bad (item 27); never, once, twice, 3 to 5 times, 6 times or more (item 28)

Reliability

Psychometric properties of the MetabQoL 1.0 scales and their correlations are summarized in Table 2 and 3. Means and skewness were higher for self-reported HrQoL than for proxy-reported HrQoL. Floor effects were not present, in contrast to ceiling effects, which were more dominant in self-reports than in proxy reports. Overall, reliability in terms of internal consistency was acceptable to excellent throughout all scales and total scores with a

range of Cronbach's α = 0.70 – 0.93, which was generally higher in proxy reports than in self-reports. All scale intercorrelations of the MetabQoL 1.0 were significant, ranging *r* = 0.60 – 0.96.

Table 8: Psychometric properties of the MetabQoL 1.0 questionnaire

	Descriptive statistics							**Reliability**
Scale	**N Items**	**Mean**	**SD**	**Median**	**Skew-ness**	**% Floor**	**% Ceiling**	**Cronbach's α**
		Self Proxy	Self Proxy	Self Proxy	Self Proxy	Self Proxy	Self Proxy	Self Proxy
Physical	13	81.68 69.92	14.70 20.75	84.16 71.15	-0.92 -0.78	0 / 0	13.2 2.4	0.77 0.90
Mental	6	85.42 71.63	15.43 20.58	89.58 77.08	-1.36 -0.27	0 / 0	23.7 9.5	0.70 0.81
Social	7	86.47 72.87	15.60 20.22	92.86 73.21	-1.19 -0.36	0 / 0	26.3 14.3	0.70 0.81
Total score	**26**	**83.83** **71.11**	**13.39** **18.68**	**87.98** **71.15**	**-0.95** **-0.32**	**0 / 0**	**5.3** **2.4**	**0.88** **0.93**
Disease-severity	2	81.25 75.30	21.89 26.69	87.50 87.50	-1.34 -1.12	0 / 0	39.5 31.0	

Validity

Convergent validity between the MetabQoL 1.0 and PedsQL / DISABKIDS was present and generally higher for the DISABKIDS than for the PedsQL (Table 4). Correlations were not limited to corresponding scales but also present between non-corresponding scales (e.g. MetabQoL 1.0 physical scale with PedsQL scales).

3.5. Discussion

This study presents the development process of the first disease-specific HrQoL questionnaire for paediatric patients with IT-IEM, the MetabQoL 1.0. The content validity of the questionnaire in general was ensured by involving patients and their parents in focus group interviews at the very beginning of the questionnaire development process (Zeltner et al., 2016). Questions for self- and proxy-assessment were constructed based on statements from the focus groups. Cognitive debriefing was performed to further refine and focus the items of the questionnaire and to gain a first impression concerning the practical applicability of the instrument. Testing of the questionnaire in a larger sample of IT-IEM patients was conducted to analyse its psychometric properties.

Table 9: Scale intercorrelations of the MetabQoL 1.0

Scales	**correlation coefficient**
	self / proxy
Physical - Mental	0.67* / 0.75*
Mental - Social	0.60* / 0.77*
Social - Physical	0.66* / 0.77*
Total score - Physical	0.96* / 0.95*
Total score - Mental	0.78* / 0.86*
Total score - Social	0.79* / 0.90*
Severity – Physical	0.53* / 0.57*
Severity – Mental	0.48 * / 0.41*
Severity - Social	0.48* / 0.55*
Severity – Total score	0.55* / 0.57*

*$p < 0.05$

Reliability in terms of internal consistency was acceptable to excellent for all scales and total scores. A general tendency towards high HrQoL was observed. This is consistent with data from other disease-specific questionnaires (Bullinger et al., 2015; Regnault et al., 2015). Correlation with the PedsQL and DISABKIDS scales was investigated to examine concurrent validity. Correlations in a medium range indicated that, beyond measuring the construct of HrQoL in general, the MetabQoL 1.0 – as intended – adds specific content and information. This result underscores the benefit of this disease-specific questionnaire. As expected, correlations with the chronic-generic instrument, DISABKIDS, were higher than with the generic instrument, PedsQL. Since the DISABKIDS specifically addresses a population with health conditions, conceptualization of HrQoL was closer to the MetabQoL 1.0. Nevertheless, due to its more specific content we hypothesise that the MetabQoL 1.0 will be more responsive to disease-related changes than the chronic-generic DISABKIDS (S. Wiebe et al., 2003) and thus most valuable for clinical practice and research settings. This hypothesis will be followed-up in long-term studies.

Generally, the results of proxy assessment were more favourable in terms of psychometric validity than the results of self-assessment. Self-assessment revealed higher means, increased skewness, lower reliability scores, and considerable ceiling effects for the mental and social scales. The modality of data collection may have influenced the answers; parents completed the questionnaires independently while children were interviewed. The focus groups performed at the beginning of the questionnaire's development allowed space to freely express and discuss opinions and feelings, encouraged by exchange with other affected patients. The standardized questionnaire interview is a less open communication situation and may have favoured socially desirable answers. This idea is supported by the observation

that, in contrast to focus group interviews, where stigmatization was a central topic (Zeltner et al. 2016), patients neglected this issue in the individual interview situation.

Table 10: Correlation coefficients between the MetabQoL 1.0 and the PedsQL (generic) / DISABKIDS (chronic-generic)

		PedsQL						**DISABKIDS**						
								Physical		Mental		Social		
		Physical	Emotional	Social	School	Psychosocial	Total	Limitation	Medication	Independence	Emotion	Inclusion	Exclusion	Total
MetabQoL 1.0 self-report*[1]	Physi-cal	0.36*	0.43*	0.44*	0.41*	0.57*	0.52*	0.59*	0.57*	0.57*	0.55*	0.41*	0.47*	0.70*
	Mental	0.20	0.34*	0.23	0.43*	0.47*	0.36*	0.50*	0.57*	0.57*	0.69*	0.41*	0.53*	0.69*
	Social	0.33*	*0.47	0.28	0.26	0.42*	0.40*	0.53*	0.47*	0.53*	0.56*	0.27	0.43*	0.57*
	Total	0.37*	0.46*	0.45*	0.41*	0.57*	0.52*	0.63*	0.64*	0.63*	0.61*	0.43*	0.52*	0.75*
MetabQoL 1.0 proxy-report	Physi-cal	0.62*	0.51*	0.63*	0.52*	0.69*	0.72*	0.84*	0.62*	0.65*	0.67*	0.57*	0.74*	0.79*
	Mental	0.45*	0.60*	0.59*	0.47*	0.67*	0.62*	0.68*	0.79*	0.58*	0.86*	0.52*	0.86*	0.84*
	Social	0.67*	0.61*	0.72*	0.46*	0.73*	0.75*	0.82*	0.57*	0.73*	0.71*	0.70*	0.76*	0.85*
	Total	0.63*	0.59*	0.71*	0.53*	0.75*	0.75*	0.86*	0.72*	0.71*	0.78*	0.65*	0.83*	0.89*

*$p < 0.05$

*[1] Sample size for convergent validity analysis was n = 37 in self-report (n=1 excluded due to complete missing of DISABKDIS and PedsQL scores) and thereby different from all other psychometric analyses

Higher self-ratings than proxy-ratings of children's HrQoL in health care are well known from the literature (Eiser & Jenney, 2007; Jamiolkowski et al., 2016). Children have a more intuitive, spontaneous view of a situation than adults and a tendency towards extreme answers (Chambers, 2002). Furthermore, the effects of fatigue may be more prominent in children and adolescents than in adults and may have led to a lack of concentration during the interviews. This assumption is supported by the results of the cognitive debriefing, which emphasized the necessity of an interviewer guiding the patients through the questionnaire booklet to maintain concentration. Some IT-IEM patients have neurocognitive deficits, and their chronological age may not fully reflect their developmental age and concentration abilities. To reduce this bias, the questionnaire was kept as short as possible, with 28 items after psychometric evaluation. Furthermore, the more comprehensible 10-item smiley version of

the MetabQoL 1.0 instrument for patients younger than 8 years, which is currently under development, may also prove useful in older patients with cognitive impairment.

Notably, 83% of the participating parents were female. In research about paediatric patients, higher representation of mothers compared to fathers is a well-known phenomenon (Goldstein et al., 2013) and may limit the generalisability of parent-reports.

The pattern of correlation between the MetabQoL 1.0 scales and the PedsQL and DISABKIDS scales showed not only correlations between corresponding scales of the three instruments but also correlations between non-corresponding scales. Furthermore, correlations were observed between total score, physical, mental, and social scales of the MetabQoL 1.0. Highest correlations were found between physical HrQoL and the total score, which is, however, partly due to the large number of items these scores share. Overall, these findings lead to the hypothesis that there may be only a single dimension behind the items of the MetabQoL 1.0. The concept of the classical three dimensions of HrQoL is under discussion, and others have proposed the sole use of a single total HrQoL score (Solans et al., 2008). Particularly in IT-IEM, the influence of the disease on patients' lives may be global. Physical aspects such as diet have a strong influence on social and mental aspects (feeling different or socially excluded). IT-IEM predominantly affect the brain. Therefore, cognitive functioning is strongly associated with the physical dimension. This association seems specific and is not present in the majority of generic HrQoL questionnaires for children (Rajmil et al., 2004) in which cognitive and emotional functioning constitute an independent mental dimension.

Factor analysis, which might have elucidated the structure of the MetabQoL 1.0 in more detail, could not be performed due to the sample size (MacCallum, Widaman, Zhang, & Hong, 1999). Although the international character of this study increased sample size, the diseases are rare, and large patient samples can only be gathered over time. Therefore, the questionnaire will be translated to be applied in larger samples in the near future. Further psychometric exploration will also include analyses of criterion validity, which was not addressed in this study. Criterion validity refers to the ability of a questionnaire to distinguish between different groups of patients. Furthermore, a larger sample may allow providing normative data. Normative data form the basis to compare between patients and to describe an individual's position within the reference group, which clearly is of long-term scientific interest. For now, the MetabQoL 1.0 is a tool to identify profiles of concerns and strains an individual patient experiences and opens the field for targeted clinical counselling. Furthermore, changes of a patient's HrQoL over time or under different treatment conditions can be monitored. These uses are not bound to normative data.

The MetabQoL 1.0 may be applied in clinical practice as well as in research, especially to detect changes in HrQoL over time. In clinical practice, monitoring HrQoL over time facilitates the identification of patients' needs and emotional and social aspects of the disease, which may not easily be detected in clinical routine. Notably, impaired social HrQoL has been shown for IT-IEM before (Fabre et al., 2013). Interestingly, the use of HrQoL instruments generally improves communication between patients and the medical team, which results in enhanced patients' well-being (Velikova et al., 2004). This is of particular importance during transitional phases such as transition to kindergarten, to school, and to adolescence (Khangura et al., 2015; Packman et al., 2012), when the impact of the disease and specific needs may change.

Considering research, disease-specific HrQoL measures are a most interesting additional approach for measuring outcome in clinical trials (S. Wiebe et al., 2003). The MetabQoL 1.0 is a promising tool for assessing disease-related HrQoL changes in IT-IEM. Furthermore, the questionnaire facilitates the exploration of predictors of HrQoL in IT-IEM patients and the development of interventions targeting patients' needs.

Conclusion

The MetabQoL 1.0 is the first psychometrically evaluated HrQoL questionnaire addressing the specific impact of IT-IEM on patients. Its targeted approach - in contrast to generic measures- renders the MetabQoL 1.0 a valuable measure in clinical and research settings. Translation into other languages and further evaluation will allow broader application of the instrument.

3.6. Intellectual property and conditions of use

Researchers or clinicians interested in using the MetabQoL 1.0© may contact the corresponding author (martina.huemer@kispi.uzh.ch).

3.7. Authors' contributions

N.A.Z. was involved in designing the study, collected and analysed the data, and drafted the manuscript. M.R.B. was involved in designing the study, contributed patient data, and critically reviewed the manuscript. A.B. R.E., D.K., S.K, C.M., S.S.B. and E.T. contributed patient data. J.Q. was involved in study design and gave advice on data analysis. P.B. was involved in coordination of the study and contributed patient data. M.A.L. was involved

in designing the study, gave advice on data collection and analysis, and critically reviewed the manuscript. M.H. provided the original concept of the study, coordinated the study, and revised the manuscript. All authors read and approved the final version of the manuscript.

3.8. Acknowledgements

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C. General Discussion

1. Summary of the results

The objective of this dissertation was to develop and psychometrically evaluate the first disease-specific HrQoL assessment tool for patients with IT-IEM. This was achieved utilizing a multidimensional approach, which is presented in three publications and finally the questionnaire MetabQoL 1.0. Questionnaires were constructed for two patient groups: those ranging in age from 8 to 18 years and patients younger than 8 years. Each questionnaire was created with parallel versions for patient- and proxy-responders.

A systematic literature review (first publication) laid down the foundation for this research, particularly by highlighting the need for a disease-specific instrument to assess HrQoL in this patient population (Zeltner et al., 2014). The second publication (Zeltner et al., 2016) presented the results of a systematic content analysis of focus group work with patients and parents. Statements were allocated to categories representing the issues that patients reported. The third and final manuscript presented in this thesis (Zeltner et al., in press) describes the development and evaluation process used for the first disease-specific questionnaire for paediatric IT-IEM patients from 8 to 18 years. A version of the MetabQoL 1.0 for younger patients was also developed over the course of this thesis project, and its evaluation is planned for the future. All MetabQoL 1.0 questionnaire versions developed in the project are presented in the additional materials section of this thesis. The methods and results of the three manuscripts are summarized in Table 11.

This general discussion section will first reflect on the questionnaire development process, including its strengths and limitations. Secondly, it will provide a closer look at the resulting HrQoL questionnaire, by analysing its quality. Thirdly, implications will be drawn for future research and clinical practice. The section will end with a general conclusion.

Table 11: Overview of sample, methods, and main results of the three manuscripts

Title	**Health-related quality of life, psychological adjustment, and adaptive functioning of patients with intoxication-type inborn errors of metabolism - a systematic review**
Methods	**Main inclusion criteria for articles:** Quantitative outcome regarding HrQoL, psychological adjustment, or adaptive functioning; IT-IEM patients; n > 1 **Analysis:** Systematic review
Main results	- 11 articles satisfying inclusion criteria - HrQoL: inconsistent results - Psychological adjustment and adaptive behaviour: IT-IEM patients exhibited no difference to or worse adjustment than reference populations - Risk factors: few medical and no psychosocial risk factors were assessed - Methodological limitations: Various approaches and assessment measures were used across the studies – pooling of results is not possible; no disease-specific assessment tool was identified

Title	**Living with intoxication-type inborn errors of metabolism - a qualitative analysis of interviews with paediatric patients and their parents**
Sample	N total = 45; n = 19 patients with IT-IEM; n = 26 parents Recruited age range of patients: 7-18 years (patient-report); 0 – 18 years (parent-report) Involved centres: Dusseldorf, Hamburg, Innsbruck, Zurich
Methods	**Assessment:** Focus groups and single interviews **Analysis:** Systematic content analysis
Main results	- 14 categories allocated to physical, mental, and social dimensions of HrQoL were identified - Comments regarding dietary restrictions and stigmatisation / exclusion were most often made by both patients and parents - The relative importance of categories (measured by number of statements per category) varied depending on the age of the patient or informant (patient / parent)

Title	**Development and psychometric evaluation of the MetabQoL 1.0 - a quality of life questionnaire for paediatric patients with inborn errors of metabolism**
Sample	N total = 80; n = 38 patients with IT-IEM, n = 42 parents Recruited age range patients: 8-18 years Involved centres: Dusseldorf, Hamburg, Heidelberg, Innsbruck, Zurich
Methods	**Materials:** Questionnaire booklet including MetabQoL 1.0, DISABKIDS, PedsQL **Assessment:** Face-to-face interviews (patients) or paper-pencil (parents) **Analysis:** Psychometric evaluation: item selection based on item descriptives, reliability, validity
Main results	- Item selection based on item characteristics: 28 items remaining - Reliability: Acceptable to excellent (Cronbach's α = 0.70 to 0.93) for all scales - Validity: Concurrent validity (significant correlation of scales) with DISABKIDS and PedsQL

2. Reflection of the questionnaire development process with its strengths and limitations

The MetabQoL 1.0 was developed carefully in accordance with current guidelines on patient-reported outcomes in paediatrics (Matza et al., 2013). As a first step, a systematic literature search served to clarify the current state of research in the field, including which assessment instruments have been used. Although research was found to be sparse, its increase over the last 10 years indicates growing interest in studying psychosocial outcomes in IT-IEM patients. The lack of a disease-specific assessment tool was apparent. The subsequently-developed MetabQoL 1.0 fills this gap.

To enhance the questionnaire's validity, we then sought patient and parental perspectives. Focus groups were conducted with families from four involved metabolic centres, and psychometric evaluations with families from five centres. Several authors have pointed out the importance of patient, and not only parent, involvement in HrQoL assessments (Matza et al., 2013; Solans et al., 2008). Proxy-assessments are used more commonly in paediatric than adult HrQoL research (Solans et al., 2008) and more commonly than patient- assessments when studying IT-IEM (Zeltner et al., 2014). The main reason for this may be the high degree of effort required for patient involvement. Despite this habitual practice, we strove to include as many IT-IEM patients as possible in all steps of questionnaire development and evaluation. The setting of focus groups was well suited for patient involvement, since the questions asked were readily adaptable to ensure their comprehensibility and, thereby, spur lively discussions. The presence of other patients in the focus groups also helped the children and adolescents to more freely discuss their concerns about their metabolic disease.

We also sought to provide an appropriate setting during the psychometric evaluation phase. Face-to-face interviews were conducted, with clear explanations and examples provided at the beginning of each evaluation session. Also, all interviewers were instructed to pause whenever necessary or otherwise appropriate. These measures enhanced patient involvement so that we acquired more than just parental input. This being said, the parents' perspectives yielded important additional information to our dataset during focus groups and psychometric evaluations. This was especially important for those patients who were unable to participate due to young age or severe neurocognitive impairment, a group of patients for whom data only were available via their parents.

Despite our best intentions, our aim to involve as many patients as possible during questionnaire development created several challenges relating to the age and developmental level of IT-IEM patients. The tool used for each psychometric evaluation was selected purely based on the given patient's chronological age. As such, all patients eight-years-old and older were assessed using the MetabQoL 1.0 version for older children and adolescents, even

though several IT-IEM patients had neurocognitive deficits, and certain 8-year-olds may have had difficulties coping with the more complex or abstract questions included in this questionnaire. A simpler measure with smiley-face rating scales, as developed for patients younger than eight, would likely have generated more accurate and meaningful responses in such cases. Using patient's developmental rather than chronological age to decide which questionnaire to choose would seem reasonable, particularly among patients at or near the 8-year threshold. However, determining the developmental age of each child at every participating clinic would have posed a major challenge.

Furthermore, the choice of patient interview modality used might have introduced its own errors and biases. HrQoL ratings by patients were higher than expected, especially for the social scale. Higher HrQoL scores during self-assessments have been well described in the literature (Bullinger et al., 2013; Regnault et al., 2015), and this might also occur, potentially even exacerbated, during face-to-face interviews. Thus, the setting itself might have created some degree of social desirability bias. Patients reported few social problems during the MetabQoL 1.0 interviews, contrary to the focus group discussions. Standardised face-to-face interviews might have been viewed as a less open communication scenario than focus group discussions, wherein patients exchanging experiences might have helped some to speak more openly about their problems. Reporting few social problems might be rooted in a child's or adolescent's desire to represent him- or herself as popular and liked by friends. Similarly, youths might have a tendency to want to present themselves as brave to their interviewer (e.g., not afraid of blood tests; not bothered by having to take medication). A more accurate account of their feelings might be obtained in the more anonymous setting of a written questionnaire, as it was done during proxy-assessments with parents. On the other hand, in-person interviews were deemed more feasible for children, since the interviewer could answer any questions the patients had about the questionnaire content, thereby facilitating their responses. In the end, we chose to enhance survey feasibility at the risk of increasing social desirability bias.

Any study on a rare disease faces challenges due to both the small research community and the limited patient population. Efforts were therefore made from the beginning to attain support from a wide range of researchers beyond national borders. Metabolic centres in Austria and Germany were found for collaboration. Participating research physicians were crucial to patient recruitment, and furthermore provided fruitful input that served to enhance the study methodologically. To strengthen the theoretical background of test development, we engaged in lively exchanges with researchers spearheading the DISABKDIS and QoLISSY projects (Bullinger et al., 2013; The DISABKIDS Group Europe, 2006), who provided ample valuable experience developing questionnaires.

Despite these collaborative efforts, the major limitations associated with questionnaire development still pertain to the small sample of patients. The underlying reason for this, of course, is the rarity of the diseases of interest, which could not be fully offset, even with multiple centres recruiting subjects. Since the MetabQoL 1.0 was solely developed in German, the patient population available to contribute to its development and evaluation also was limited to German speakers. Parallel development of the questionnaire in several languages, as done elsewhere (Regnault et al., 2015; The DISABKIDS Group Europe, 2006; The KIDSCREEN Group Europe, 2006) would have helped to overcome this problem. However, the scope of the project would have needed to be expanded considerably. The first publication in this thesis (Zeltner et al., 2014) has already described the problematic impact of small sample sizes in previously-published studies. The focus groups could also have benefited from additional participants, though smaller subject samples are considered less of an issue with qualitative than quantitative analysis, as conducted here. The representativeness of the sample was deemed more critical. In our study, the sample's representativeness — in terms of patient characteristics like age, gender, and general medical condition (e.g., tube feeding, physical limitations like difficulty walking) — was ensured by the recruiting physicians.

Ultimately, the limited sample size was most problematic during the psychometric evaluation of the instrument. All data collected were stratified into the two versions of the MetabQoL 1.0 created (for patients < 8 versus 8 to 18 years). This aggravated the problem of sample size. In the end, we were forced to forego evaluating the questionnaire version for younger children psychometrically, limiting our analysis (as described in the third manuscript) to the self- and proxy-versions of the MetabQoL 1.0 for older children and adolescents. Even so, small numbers still hampered some statistical procedures. One casualty of the low numbers was our intended confirmatory and exploratory factor analysis to shed light on the dimensionality of our questionnaire, since it failed to reveal meaningful results. In all likelihood, this relates to the sensitivity of factor analysis to sample size (MacCallum et al., 1999). Several guidelines recommend that larger samples are best for factor analysis, though some have argued that factor analysis can be performed on samples with as few as 60 subjects, if the circumstances are favourable (e.g., with communality ratings of 0.60 – 0.80 between items) (Bühner, 2011). Unfortunately, despite our efforts, our sample size even fell below these tolerance guidelines, and all our attempts at factor analysis were unsuccessful.

3. Reflection of the quality of the MetabQoL 1.0

The MetabQoL 1.0 questionnaire was the primary intended outcome of this thesis. Hence, its psychometric evaluation and how well it performed in terms of quality criteria will be discussed based on the criteria presented in the introduction. The main quality criteria (objectivity, reliability and validity) and other auxiliary quality criteria are listed again in Figure 9. Also indicated is whether the MetabQoL 1.0 for patients from 8 to 18 years either successfully satisfied or failed to adequately satisfy each individual criterion.

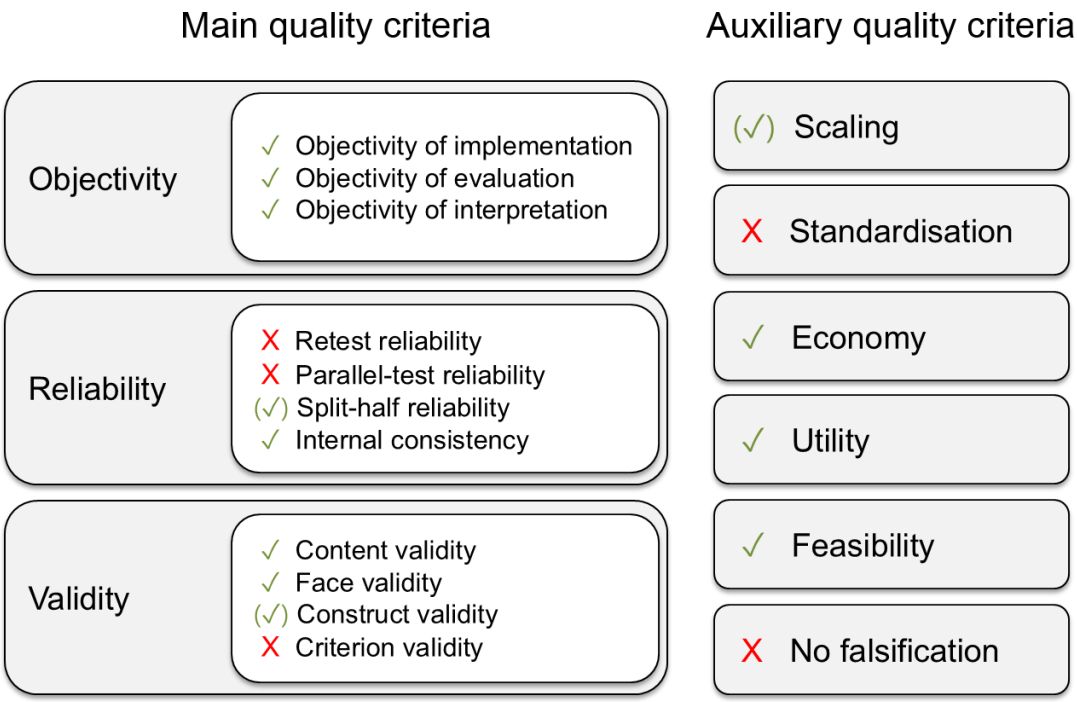

Figure 9: Quality criteria tested on the MetabQoL 1.0 for patients from 8 to 18 years

Green check marks indicate that the instrument successfully satisfied a criterion, while red crosses indicate failure to adequately satisfy a criterion

The MetabQoL 1.0 satisfied the main quality criterion called *objectivity*. Standardisation of the questionnaire and detailed instructions for interviewers ensured objectivity to as great a degree as possible. This was of utmost importance, since the interviews were mostly completed at participant homes, so that the interview surroundings were not identical from one subject to the next. Evaluation and interpretation of the questionnaire was performed in a standardised way by the author of this thesis. It is crucial to note that a detailed manual is being drafted for use by other research groups or clinicians who choose to use the MetabQoL 1.0 to ensure that objectivity is maintained.

Reliability was investigated by assessing the questionnaire's internal consistency, and all scales satisfied this criterion. Moreover, since internal consistency can be considered an extension of split-half reliability, this criterion also was deemed satisfied. Test-retest reliability was not evaluated, since HrQoL is a dynamic construct that is subject to change over time, which renders the relevance of test-retest reliability debatable. As such, finding low test-retest reliability could just as likely be caused by a real change in a patient's HrQoL as by one or more inaccurate measurements. Moreover, assessing test-retest reliability would have required a second evaluation, causing undue stress and creating unnecessary burdens on participating patients and parents. The same applies to parallel-test reliability. For all these reasons, the questionnaire's internal consistency was the only reliability criterion actively measured, and this was found to be adequate.

In contrast, several *validity* constructs were evaluated. Content validity was verified by experts in the field, as suggested by others (Moosbrugger & Kelava, 2012). The multidisciplinary team that developed the questionnaire was an expert panel, all of whom contributed to ensuring that the questionnaire's content was relevant to the issues of concern. Even more importance might be attributed to the opinions of patients and parents who participated in the focus groups. Their subjective experiences with the disease included a broad range of ways in which the disease impacted them, allowing us to create a tool that was deeply rooted in HrQoL as previously defined (Varni et al., 1999). In this way, the instrument's content validity was verified by all major stakeholders.

The criterion face validity, which refers to the extent that a questionnaire appears valid to laypersons at first appearance (Moosbrugger & Kelava, 2012), can be considered satisfied, since the questions were believed relevant during pilot testing, and acceptance was good overall in both the pilot test and psychometric evaluation.

Making a judgement about construct validity is more complex. Significant correlations between the MetabQoL 1.0 and generic HrQoL scale scores suggest good concurrent validity. However, exploration of the questionnaire's dimensionality, usually possible with factor analysis procedures, could not be performed because of the small sample size. This issue will be discussed further in the following sections considering directions for future research.

Criterion validity also was not assessed in the evaluation of the MetabQoL 1.0. A test is said to have criterion validity if the test score can predict a "criterion" beyond the test situation (Moosbrugger & Kelava, 2012). In the case of disease-specific HrQoL, the physical HrQoL subscale could possibly be associated with the severity of the disease. Other studies have identified such things as group differences as a means to address criterion validity. For example, the quality of life in short-stature youth questionnaire (QoLISSY) (Bullinger et al., 2013) is a condition-specific instrument whose score significantly distinguishes between

groups of different height. However, such different severity groups are difficult to form among IT-IEM patients. Required tube feeding might be viewed as one possible criterion with which to distinguish different levels of disease severity in IT-IEM patients. However, tube feeding may sometimes be necessary in patients having major problems with food intake, but who are otherwise relatively intact; while others with severe neurological or other manifestations of disease might still be able to accept food orally. Another criterion that might be used to delineate disease severity can be seen in the last two items of the MetabQoL 1.0 questionnaire, in which severity of the disease over in the last year is asked about. However, these two items are non-objective measures, rated by the same person rating HrQoL, a rating that in our sample was strongly skewed towards a lower level of severity during questionnaire evaluation. A threshold to distinguish “more severe” and “less severe” cases could have been picked, but this in itself would need to be tested for criterion validity.

The *auxiliary criterion* pertaining to scaling can be considered at least partially satisfied, in that precise instructions exist explaining how to aggregate individual item ratings in the MetabQoL 1.0 into summation scores. However, as the dimensionality of the MetabQoL 1.0 requires further exploration, the scales could still be subject to change. Further psychometric exploration could also contribute to standardisation, which cannot be provided at this level of questionnaire development and will need a larger sample. This being said, the primary aim of disease-specific HrQoL questionnaires is not for use rendering comparisons against reference populations; the MetabQoL 1.0 questionnaire is designed for use particularly as an outcome measure in studies or in clinical settings to monitor HrQoL over time. Hence, its sensitivity to change and its specificity for disease-related issues are more critical characteristics. The sensitivity of the MetabQoL 1.0 to change has not yet been explored, but there is clear evidence that disease-specific instruments are more responsive to change than generic instruments (S. Wiebe et al., 2003).

Furthermore, the MetabQoL 1.0 is economical and feasible to use, which was ensured by shortening the questionnaire and paying considerable attention to using language and a format suitable for a paediatric population. Despite these efforts, administering the questionnaire was challenging with some children and adolescents, which could be attributed to their young age or to neuro-developmental deficits. The question of how children up to age 12 years understand health constructs remains to be clarified not only among IT-IEM patients, but in healthy children as well (Matza et al., 2013).

The last criterion to be discussed here relates to the extent to which a test result can be falsified. Potential social desirability bias, possibly exacerbated by the in-person interview data collection format, was observed in the analysis (Zeltner et al., in press). The risk that

patients might falsify their responses to provide a more socially-desirable depiction of themselves (e.g., by reporting a higher quality of life or having numerous friends) is well-known in child-reported outcomes research (Bevans et al., 2010).

4. Considerations for future research and clinical practice

4.1. Implications for future research

The MetabQoL 1.0 serves as a solid basis to be evaluated in other, larger populations. The next step to be taken includes careful translation of the questionnaire into different languages, as per appropriate guidelines (Epstein, Santo, & Guillemin, 2015). Translation of the MetabQoL 1.0 into English is in progress, and plans are already in place for both versions of the questionnaire (<8 years and 8-18 years) to be tested psychometrically in the United States. This will provide sufficient data to finally evaluate the MetabQoL 1.0 for patients younger than 8 years. Furthermore, catching up on the evaluation performed in German for the version for patients from 8 to 18 years will allow for exploration of construct validity by factor analysis. Merging data sets of different languages can be taken into account if item characteristics are comparable among different-language samples. This would generate larger samples and thus, a greater quantity of data for more detailed analysis.

Importantly, further evaluations of the MetabQoL 1.0 will allow for the current dimensionality of the HrQoL construct to be critically reviewed. At the present time, summation scores can be calculated for three scales — physical, mental and social — as well as a total score from individual item scores for the MetabQoL 1.0 for patients from 8 to 18 years. The present results of psychometric evaluation suggest that there may be only one dimension underlying the items. As elaborated in the third manuscript in this thesis (Zeltner et al., in press), this may be rooted in the very global impact IT-IEM has on patients. However, our results do not allow for us to draw any definitive conclusions. Notably, different reviews revealed a broad range of diversity in HrQoL conceptualisations and the need for research to establish a more robust theoretical background for HrQoL in general (E. Davis et al., 2006; Solans et al., 2008).

In the focus group study, parents frequently reported their own distress (Zeltner et al., 2016). Other questionnaires that seek to assess a child's HrQoL have included parent-centred questions in proxy-report versions (Bullinger et al., 2013; Regnault et al., 2015). Even though these questions are not direct indicators of the child's HrQoL, they may provide interesting insights into internal family relationships. Furthermore, by demonstrating concern regarding not just the child's but the parents' feelings, they can enhance the questionnaire's acceptability.

The MetabQoL 1.0 also facilitates future research on HrQoL in IT-IEM patients. The specific burdens of patients need to be explored. With its disease-specific content, the MetabQoL 1.0 provides ideal outcomes of interest for use in clinical trials and may be especially sensitive to disease-related changes (S. Wiebe et al., 2003), contrary to generic HrQoL

measures like the widely-used PedsQL (Varni et al., 1999). Relative to other fields of research, in which the implementation of HrQoL instruments is usual practice, the MetabQoL 1.0 will be a step towards implementation in IT-IEM research, as well. This will help us all to achieve the ultimate goal of developing medical interventions to best serve the patient, by including outcomes of importance to patients in addition to medical parameters (Bullinger, Schmidt, Petersen, Erhart, & Ravens-Sieberer, 2007).

Future research should also examine factors that influence HrQoL, as this may help to identify successful interventions. The review at the beginning of this project revealed that a number of medical, but no psychosocial predictors had yet been explored (Zeltner et al., 2014). However, psychosocial predictors may deserve special attention, as individual characteristics like level of coping skills, as well as certain family characteristics have been shown to be important predictors of HrQoL in other settings (Landolt, Grubenmann, et al., 2002; Walterfang et al., 2013). Parental well-being after a child is diagnosed with a chronic disease has been shown to be a predictor of good recovery in the child (Landolt, Ystrom, Sennhauser, Gnehm, & Vollrath, 2012).

Another interesting target for future research relates to patient adherence to diet and medication, which is desperately needed in IT-IEM patients. This responsibility has been found to be taken over by parents with very young children (Zeltner et al., 2016). Later on in childhood and during adolescence, patients usually take more and more responsibility for their health. However, it has been shown that diabetic children from 10-15 years of age exhibit peak adherence and quality of life if they perceive their mothers to be collaborative regarding their diabetes, rather than either uninvolved or controlling (D. J. Wiebe, 2005). These findings underline the importance of a family system approach when investigating HrQoL, whether that is in research or clinical practice. In the long term, monitoring HrQoL and identifying which factors contribute most to it may serve to optimize interventions and thereby render accessible the best possible care for patients and their families.

4.2. Implications for clinical practice

Clinical implications first of all include application of the MetabQoL 1.0 in clinical settings, which may provide multiple benefits. First of all, HrQoL instruments are known to facilitate communication between patients and hospital staff (Velikova et al., 2004). They may furthermore help to identify problems which are not always addressed in routine consultations (emotional and social issues), and help to monitor changes in patients' state of health and response to treatment (Higginson & Carr, 2001). One must keep in mind that

HrQoL measures were never designed to replace other biomedical measures or medical examinations; rather, they are an ideal supplement to "ensure that treatment and evaluation focus on the patient rather than the disease" (Higginson and Carr 2001, p. 1297). For a HrQoL questionnaire to be put into practice, it is of great importance that its content covers the issues of interest for patients, and that its application and interpretation are as user-friendly as possible (Higginson & Carr, 2001). Content validity was ensured during development of the MetabQoL 1.0. However, an electronic version (e.g., on a tablet) that automatically interprets the questionnaire and can be given to patients and parents in the waiting room would be ideal. This concept can be pursued in future tool development.

Some of the focus group findings have clinical implications as well. Besides generating categories of importance with which to construct our HrQoL questionnaire, the focus groups provided initial insights into the real-world problems that patients and families experience. This, in turn, not only illustrates the importance of providing better family support, but also which areas to focus on. One area of concern to many was how difficult it is to explain whatever complicated disease they are facing to others. This was found to pose a problem not only for very young children, but throughout all age groups, including parents. The metabolic department in Zurich has therefore started a project to develop and validate attractive pictorial materials, appropriate for children, to explain the genetics, biochemical basis and treatment options for metabolic diseases.

Another finding that might have clinical practice implications was that social issues were raised as a major concern in focus groups, but not during face-to-face interviews. This emphasizes the importance of offering patients the right context in which to express their feelings and concerns. In the setting of focus groups, patients were able to exchange experiences with other affected children and adolescents. Some of them stated that they really appreciated this, and that they had never had any opportunity like this before. Hence, connecting patients with support groups could be very helpful. Unfortunately, however, the number of support groups is very limited amongst rare diseases, and accessing them typically is difficult due to the lack of information and prohibitive geographical distances (Anderson, Elliott, & Zurynski, 2013).

In general, psychosocial care seems to be lacking for families with a child with a severe rare disease (Anderson et al., 2013), even though it is well-known that life-threatening conditions adversely impact psychological health and functioning among paediatric patients and their families (e.g. Landolt et al., 2012; Long & Marsland, 2011). Standards exist for psychosocial care for more common diseases like cancer (Wiener, Kazak, Noll, Patenaude, & Kupst, 2015). Such standards and guidelines include steps like integrating psychosocial profession-

als as integral team members in the hospital setting, performing routine assessments of patient's psychosocial health care needs, and providing access to psychosocial support for patients, parents, and siblings (Wiener et al., 2015). These same interventions offered for cancer patients and their families could very well be helpful for IT-IEM patients as well. As for other diseases, not only patients but their parents and other family members warrant attention, due to the known inter-dependence between a child's well-being and a variety of family characteristics (Landolt et al., 2012). This need was highlighted in our focus groups, via the large number of comments parents made about their own distress (Zeltner et al., 2016).

5. General conclusion

To our knowledge, the MetabQoL 1.0 is the first HrQoL questionnaire specifically designed for use with IT-IEM patients. It was carefully developed by reviewing existing literature and orchestrating focus group discussions with IT-IEM patients and their parents to define contents. The focus group discussions were enlightening in other ways as well, providing glimpses into ways to improve support for patients and families.

Evaluation of the questionnaire that was created was performed using a combined patient and parent sample, and revealed several robust psychometric properties of the MetabQoL 1.0, justifying its use both in research and clinical practice. Translation into other languages, testing it in other, larger IT-IEM samples, and further psychometric evaluation will help to delineate the instrument's dimensionality, potentially leading to future refinements. It is our hope that the MetabQoL 1.0 will serve as both as a means to enhance our understanding of how and in which ways these conditions most impact HrQoL; and, by doing so, to ultimately augment all aspects of care for IT-IEM patients and their families.

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Appendix

The following pages contain the questionnaires used for psychometric evaluation. Versions for patients aged from 8 to 18 years are displayed in their original length, as they were before item selection.

Questionnaire for patients from 8 to 18 years, patient-report

Fragebogen für Kinder und Jugendliche

Wir möchten gerne von Dir wissen wie es Dir mit deiner Stoffwechselkrankheit geht und wie Du Dich fühlst. Dafür haben wir uns Fragen ausgedacht und fragen Dich auch nach Schwierigkeiten, die Du mit Deiner Stoffwechselkrankheit haben könntest.

Denke bitte an **die letzten vier Wochen** zurück, wenn Du die Fragen beantwortest.

Hier kannst du ein Beispiel sehen:	nie	selten	manchmal	oft	immer
Wie häufig räumst Du Dein Zimmer auf?	☐ 0	☐ 1	☐ 2	☒ 3	☐ 4

So kannst Du das Kreuz machen, wenn Du Dein Zimmer oft aufräumst.

Über Deine Diät	nie	selten	manchmal	oft	immer	Ich muss keine Diät halten
1. Fällt es Dir schwer, Dich an Deine Diät zu halten?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2. Stört es Dich, dass Du nicht alles essen darfst, was Du willst?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
3. Stört es Dich, dass Andere essen und trinken können, was sie wollen?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
4. Stört es Dich, dass Du essen musst, obwohl Du keinen Hunger hast?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Bei den nächsten Fragen geht es um Deine Medikamente. Damit meinen wir Tabletten, Spezial-Getränke oder Spezial-Pulver (Aminosäuren).	nie	selten	manchmal	oft	immer	Ich nehme keine Medikamente
5. Stört es Dich, dass Du Medikamente nehmen musst?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
6. Stört Dich der Geschmack Deiner Medikamente?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
7. Stört es Dich, dass Du immer wieder zu bestimmten Zeiten Medikamente nehmen musst?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Über Deine Erfahrungen mit Ärzten und im Krankenhaus	nie	selten	manchmal	oft	immer
8. Stört es Dich, dass Du regelmässige Kontrollen hast?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
9. Hast Du Angst vor Blutabnahmen?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
10. Macht es Dir Sorgen, dass Du vielleicht notfallmässig ins Krankenhaus musst?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
11. Macht es Dir Sorgen, dass Du wegen einer Stoffwechselentgleisung im Krankenhaus bleiben musst?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
12. Machst Du Dir Sorgen, dass Du eine Stoffwechselentgleisung haben könntest?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
13. Machst Du Dir Sorgen um Deine Blutwerte?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

Über die Schule/ Lehre	nie	selten	manchmal	oft	immer
14. Stört Dich Deine Stoffwechselkrankheit beim Lernen?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
15. Hast Du wegen Deiner Stoffwechselkrankheit Probleme in der Schule/ Lehre mitzukommen?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
16. Kannst Du wegen Deiner Stoffwechselkrankheit in der Schule/ Lehre weniger gut aufpassen?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

Über Deinen Alltag mit der Stoffwechselkrankheit	nie	selten	manchmal	oft	immer	Keine Beschwerden in diesem Bereich
17. Schränkt Dich Deine Stoffwechselkrankheit im Alltag ein?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
18. Stört Dich Deine Stoffwechselkrankheit beim Spielen oder anderen Aktivitäten?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
19. Stört es Dich, dass Du Dich nicht so gut bewegen kannst wie Andere?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
20. Stört es Dich, dass Du beim Anziehen Hilfe brauchst?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
21. Stört es Dich, dass Du Hilfe brauchst, wenn Du auf die Toilette musst?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
22. Stört es Dich, dass Du im Turnunterricht/ Sport nicht so gut mitmachen kannst wie Andere?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
23. Stört es Dich, dass Du schnell müde wirst?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
24. Stört es Dich, dass Dir öfters übel ist?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
25. Stört es Dich, dass Du öfters erbrechen musst?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
26. Stört es Dich, dass Du eine Sonde hast?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
27. Stört es Dich, wie Du mit deiner Sonde aussiehst?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Über Deine Freunde und Deine Familie	nie	selten	manchmal	oft	immer
28. Fällt es Dir wegen Deiner Stoffwechselkrankheit schwer, Freunde zu finden?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
29. Hast Du wegen Deiner Stoffwechselkrankheit weniger Freunde?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
30. Hast Du wegen Deiner Stoffwechselkrankheit Probleme, mit Freunden etwas zu unternehmen?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
31. Sind Andere wegen Deiner Stoffwechselkrankheit weniger gern mit Dir befreundet?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
32. Stört es Dich, dass Deine Eltern oder andere aus Deiner Familie besonders um dich besorgt sind wegen der Stoffwechselkrankheit?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
33. Ärgert es Dich, dass Dir Deine Eltern oder andere aus Deiner Familie wegen der Stoffwechselkrankheit Dinge verbieten?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
34. Unterstützt Dich Deine Familie bezüglich der Stoffwechselkrankheit?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

Über Deine Gefühle	nie	selten	manchmal	oft	immer
35. Bist Du zufrieden?	0	1	2	3	4
36. Bist Du glücklich?	0	1	2	3	4
37. Machst Du Dir Sorgen wegen Deiner Stoffwechselkrankheit?	0	1	2	3	4
38. Bist Du traurig, weil Du eine Stoffwechselkrankheit hast?	0	1	2	3	4
39. Bist Du wütend, dass Du eine Stoffwechselkrankheit hast?	0	1	2	3	4
40. Fühlst Du Dich wegen Deiner Stoffwechselkrankheit einsam?	0	1	2	3	4
41. Fühlst Du Dich wegen Deiner Stoffwechselkrankheit nicht normal?	0	1	2	3	4
42. Hast Du wegen Deiner Stoffwechselkrankheit Angst vor der Zukunft?	0	1	2	3	4

Über Deine Erfahrungen mit der Stoffwechselkrankheit	nie	selten	manchmal	oft	immer
43. Stört es Dich, dass man wegen Deiner Stoffwechselkrankheit anders mit Dir umgeht?	0	1	2	3	4
44. Stört es Dich, dass man Dir wegen Deiner Stoffwechselkrankheit weniger zutraut?	0	1	2	3	4
45. Stört es Dich, dass viele Menschen Deine Krankheit nicht verstehen?	0	1	2	3	4
46. Machen sich andere über Dich lustig wegen Deiner Stoffwechselkrankheit?	0	1	2	3	4
47. Ärgern Dich Andere wegen Deiner Stoffwechselkrankheit?	0	1	2	3	4
48. Wirst Du wegen Deiner Stoffwechselkrankheit ausgeschlossen?	0	1	2	3	4
49. Wirst Du wegen Deiner Stoffwechselkrankheit komisch angeschaut?	0	1	2	3	4
50. Stört es Dich, wenn andere Menschen Mitleid mit Dir haben?	0	1	2	3	4

Über Deine Stoffwechselkrankheit in den letzten 12 Monaten

51. Wie stark waren Deine Probleme mit der Stoffwechselkrankheit in den letzten 12 Monaten?
☐ 0 sehr wenig ☐ 1 wenig ☐ 2 mittelmässig ☐ 3 stark ☐ 4 sehr stark

52. Wie oft bist Du in den letzten 12 Monaten notfallmässig im Krankenhaus aufgenommen worden?
☐ 0 nie ☐ 1 1 Mal ☐ 2 2 Mal ☐ 3 3-5 Mal ☐ 4 6 Mal oder mehr

Questionnaire for patients from 8 to 18 years, parent-report

Lebensqualität Ihres Kindes - 1

Wir möchten gerne erfahren, wie es Ihrem Kind mit seiner Stoffwechselkrankheit geht und wie es sich fühlt. Auf den nächsten Seiten fragen wir daher nach Schwierigkeiten und Einschränkungen, die bei Stoffwechselkrankheiten auftreten können. Bitte geben Sie bei jeder Frage die am besten zutreffende Antwort an. Denken sie dabei an die letzten 4 Wochen zurück wenn nichts anderes vermerkt ist.

Über Die Diät Ihres Kindes	nie	selten	manchmal	oft	immer	Kind muss keine Diät halten
1. Fällt es Ihrem Kind schwer, sich an seine Diät zu halten?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2. Stört es Ihr Kind, dass es nicht alles essen darf, was es will?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
3. Stört es Ihr Kind, dass Andere essen und trinken können, was sie wollen?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
4. Stört es Ihr Kind, dass es essen muss, obwohl es keinen Hunger hat?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Bei den nächsten Fragen geht es um die Medikamente Ihres Kindes. Damit meinen wir Tabletten, Spezial-Getränke oder Spezial-Pulver (Aminosäuren).	nie	selten	manchmal	oft	immer	Kind nimmt keine Medikamente
5. Stört es Ihr Kind, dass es Medikamente nehmen muss?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
6. Stört Ihr Kind der Geschmack seiner Medikamente?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
7. Stört es Ihr Kind, dass es immer wieder zu bestimmten Zeiten Medikamente nehmen muss?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Über die Erfahrungen Ihres Kindes mit Ärzten und im Krankenhaus	nie	selten	manchmal	oft	immer
8. Stört es Ihr Kind, dass es regelmässige Kontrollen hat?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
9. Hat Ihr Kind Angst vor Blutabnahmen?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
10. Macht es Ihrem Kind Sorgen, dass es vielleicht notfallmässig ins Krankenhaus muss?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
11. Macht es Ihrem Kind Sorgen, dass es wegen einer Stoffwechselentgleisung im Krankenhaus bleiben muss?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
12. Macht sich Ihr Kind Sorgen, dass es eine Stoffwechselentgleisung haben könnte?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
13. Macht sich Ihr Kind Sorgen um seine Blutwerte?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

Über die Schule/ Lehre	nie	selten	manchmal	oft	immer
14. Stört die Stoffwechselkrankheit Ihr Kind beim Lernen?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
15. Hat Ihr Kind wegen seiner Stoffwechselkrankheit Probleme in der Schule/ Lehre mitzukommen?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
16. Kann Ihr Kind wegen seiner Stoffwechselkrankheit in der Schule/ Lehre weniger gut aufpassen?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

Über den Alltag Ihres Kindes mit der Stoffwechselkrankheit	nie	selten	manchmal	oft	immer	Keine Beschwerden in diesem Bereich
17. Schränkt die Stoffwechselkrankheit Ihr Kind im Alltag ein?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
18. Stört die Stoffwechselkrankheit Ihr Kind beim Spielen oder anderen Aktivitäten?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
19. Stört es Ihr Kind, dass es sich nicht so gut bewegen kann wie Andere?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
20. Stört es Ihr Kind, dass es beim Anziehen Hilfe braucht?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
21. Stört es Ihr Kind, dass es Hilfe braucht, wenn es auf die Toilette muss?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
22. Stört es Ihr Kind, dass es im Turnunterricht/ Sport nicht so gut mitmachen kann wie Andere?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
23. Stört es Ihr Kind, dass es schnell müde wird?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
24. Stört es Ihr Kind, dass ihm öfters übel ist?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
25. Stört es Ihr Kind, dass es öfters erbrechen muss?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
26. Stört es Ihr Kind, dass es eine Sonde hat?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
27. Stört es Ihr Kind, wie es mit seiner Sonde aussieht?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Über die Freunde und Familie Ihres Kindes	nie	selten	manchmal	oft	immer
28. Fällt es Ihrem Kind wegen seiner Stoffwechselkrankheit schwer, Freunde zu finden?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
29. Hat Ihr Kind wegen seiner Stoffwechselkrankheit weniger Freunde?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
30. Hat Ihr Kind wegen seiner Stoffwechselkrankheit Probleme, mit Freunden etwas zu unternehmen?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
31. Sind Andere wegen der Stoffwechselkrankheit Ihres Kindes weniger gern mit ihm befreundet?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
32. Stört es Ihr Kind, dass seine Eltern oder andere aus der Familie besonders um sie/ ihn besorgt sind?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
33. Ärgert es Ihr Kind, dass ihm seine Eltern oder andere aus seiner Familie wegen der Stoffwechselkrankheit Dinge verbieten?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
34. Fühlt sich Ihr Kind durch seine Familie bezüglich der Stoffwechselkrankheit unterstützt?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

Über die Gefühle Ihres Kindes	nie	selten	manchmal	oft	immer
35. Ist Ihr Kind zufrieden?	0	1	2	3	4
36. Ist Ihr Kind glücklich?	0	1	2	3	4
37. Macht sich Ihr Kind Sorgen wegen seiner Stoffwechselkrankheit?	0	1	2	3	4
38. Ist Ihr Kind traurig, weil es eine Stoffwechselkrankheit hat?	0	1	2	3	4
39. Ist Ihr Kind wütend, dass es eine Stoffwechselkrankheit hat?	0	1	2	3	4
40. Fühlt sich Ihr Kind wegen seiner Stoffwechselkrankheit einsam?	0	1	2	3	4
41. Fühlt sich Ihr Kind wegen seiner Stoffwechselkrankheit nicht normal?	0	1	2	3	4
42. Hat Ihr Kind wegen seiner Stoffwechselkrankheit Angst vor der Zukunft?	0	1	2	3	4

Über die Erfahrungen Ihres Kindes mit der Stoffwechselkrankheit	nie	selten	manchmal	oft	immer
43. Stört es Ihr Kind, dass man wegen seiner Stoffwechselkrankheit anders mit ihm umgeht?	0	1	2	3	4
44. Stört es Ihr Kind, dass man ihm wegen seiner Stoffwechselkrankheit weniger zutraut?	0	1	2	3	4
45. Stört es Ihr Kind, dass viele Menschen seine Krankheit nicht verstehen?	0	1	2	3	4
46. Machen sich andere über Ihr Kind lustig wegen seiner Stoffwechselkrankheit?	0	1	2	3	4
47. Ärgern Andere Ihr Kind wegen seiner Stoffwechselkrankheit?	0	1	2	3	4
48. Wird Ihr Kind wegen seiner Stoffwechselkrankheit ausgeschlossen?	0	1	2	3	4
49. Wird Ihr Kind wegen seiner Stoffwechselkrankheit komisch angeschaut?	0	1	2	3	4
50. Stört es Ihr Kind, wenn andere Menschen Mitleid mit ihm haben?	0	1	2	3	4

Über die Stoffwechselkrankheit Ihres Kindes in den letzten 12 Monaten

51. Wie stark waren die Probleme Ihres Kindes mit der Stoffwechselkrankheit in den letzten 12 Monaten?
☐ 0 sehr wenig ☐ 1 wenig ☐ 2 mittelmässig ☐ 3 stark ☐ 4 sehr stark

52. Wie oft ist Ihr Kind in den letzten 12 Monaten notfallmässig im Krankenhaus aufgenommen worden?
☐ 0 nie ☐ 1 1 Mal ☐ 2 2 Mal ☐ 3 3-5 Mal ☐ 4 6 Mal oder mehr

Questionnaire for patients from 4 to 7 years, patient-report

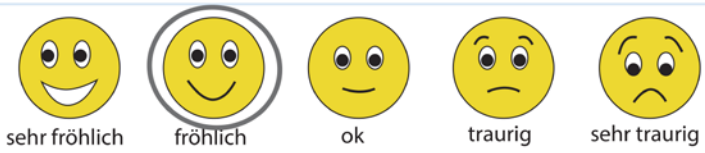
Fragebogen für Kinder

Wir möchten gerne von Dir wissen wie es Dir mit deiner Stoffwechselkrankheit geht und wie Du Dich fühlst. Dafür haben wir uns Fragen ausgedacht und fragen Dich auch nach Schwierigkeiten, die Du mit Deiner Stoffwechselkrankheit haben könntest. Ich lese dir nun die Fragen vor. Als Antwort zeigst Du bitte auf eines der Gesichter, je nachdem, welches Problem Du damit hast.

Denke bitte an **die letzten vier Wochen** zurück, wenn Du die Fragen beantwortest.

Hier kannst du ein Beispiel sehen:

Wie fühlst Du Dich, wenn Du ins Schwimmbad gehst?



Dieses Gesicht kannst Du umkreisen, wenn du dich fröhlich fühlst, wenn du ins Schwimmbad gehst.

1. Wie fühlst Du Dich, wenn Du nicht alles essen darfst, was Du gerne willst?

2. Wie fühlst Du Dich, wenn Du etwas essen musst, obwohl Du keinen Hunger hast?

3. Wie fühlst Du Dich, wenn Du Medikamente nimmst? (z.B. Tabletten, Pulver, spezielle Drinks, Aminosäuremischungen)

4. Hast Du eine Sonde?

Wenn ja, wie fühlst Du Dich, wenn Du an Deine Sonde denkst?

5. Wie fühlst Du Dich, wenn Du zum Arzt oder ins Krankenhaus gehst?

6. Wie fühlst Du Dich, wenn man Dir Blut abnehmen muss?

7. Kannst Du gleich gut herumlaufen und rennen wie andere Kinder?

ja nein

0 1

Wenn nein, wie fühlst Du Dich dabei?

8. Wie fühlst Du Dich meistens?

9. Wie fühlst Du Dich, wenn Du mit Deiner Familie zusammen bist?

10. Wie fühlst Du Dich, wenn Du mit anderen Kindern zusammen bist?

Questionnaire for patients from 2 to 7 years, parent-report

Lebensqualität Ihres Kindes - 1

Wir möchten gerne erfahren, wie es Ihrem Kind mit seiner Stoffwechselkrankheit geht und wie es sich fühlt. Auf den nächsten Seiten fragen wir daher nach Schwierigkeiten und Einschränkungen, die bei Stoffwechselkrankheiten auftreten können. Bitte geben Sie bei jeder Frage die am besten zutreffende Antwort an. Denken sie dabei an die letzten 4 Wochen zurück wenn nichts anderes vermerkt ist.

Hier können Sie ein Beispiel sehen:

Wie fühlt sich Ihr Kind, wenn es ins Schwimmbad geht?

Dieses Gesicht können Sie umkreisen, wenn sich Ihr Kind fröhlich fühlt, wenn es ins Schwimmbad geht.

1. Wie fühlt sich Ihr Kind, wenn es nicht alles essen darf, was es gerne möchte?

2. Wie fühlt sich Ihr Kind, wenn es etwas essen muss, obwohl es keinen Hunger hat?

3. Wie fühlt sich Ihr Kind, wenn es Medikamente einnimmt? (z.B. Tabletten, Pulver, spezielle Drinks, Aminosäuremischungen)

4. Hat Ihr Kind eine Sonde?

Wenn ja, wie fühlt es sich, wenn es an seine Sonde denkt?

5. Wie fühlt sich Ihr Kind, wenn es zum Arzt oder ins Krankenhaus geht?

6. Wie fühlt sich Ihr Kind, wenn man ihm Blut abnehmen muss?

7. Kann Ihr Kind gleich gut herumlaufen und rennen wie andere Kinder?

ja ☐ 0 nein ☐ 1

Wenn nein, wie fühlt sich Ihr Kind dabei?

8. Wie fühlt sich Ihr Kind meistens?

9. Wie fühlt sich Ihr Kind, wenn es mit seiner Familie zusammen ist?

10. Wie fühlt sich Ihr Kind, wenn es mit anderen Kindern zusammen ist?

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Curriculum Vitae

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Education

2015 – present	Universities of Basel, Bern, and Zürich Post gradual education in psychotherapy for children and adolescents
2013 – 2016	Children's Hospital and Institute of Psychology, University of Zürich PhD studies, project: Development and evaluation of a quality of life questionnaire for children and adolescents with intoxication-type inborn errors of metabolism (Prof.Landolt, Prof. Bodenmann, Prof. Baumgartner)
2013	University of Zürich Master of Science in Psychology Psychology (major), Biology (minor) Health and Clinical Psychology Master thesis: Psychosocial Aspects in Endometriosis and Chronic Pelvic Pain (Prof. Ehlert)
2010	University of Zürich Bachelor of Science in Psychology Psychology (major), Biology (minor)
2008 – 2009	Université Paris Denis Diderot Erasmus exchange year Courses in Neurobiology und Chemistry

Professional experience

07 – 12/2011	Clienia Privatklinik Littenheid Internship, department of psychotherapy for young adults Based on cognitive behavioural therapy: DBT and schema therapy
08 – 10/2009	University Children's Hospital Zürich Research internship in neurobiology (Prof. Stöckli) fMRI-study: dyscalculia in children

06 – 08/2009	University of Zürich Student research assistant for stress-studies (Prof. Ehlert)
04/2006	Regional hospital Uster Internship in nursing care
08/2005 – 02/2006	Kindergarten and primary school Stadel Assistant teacher

Awards

Poster prize for Poster presentation at the Children's Research Centre Retreat (2015, October) entitled *Living with intoxication-type inborn errors of metabolism - a qualitative analysis of interviews with paediatric patients and their caregivers*

Publications

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Huemer, M., Zeltner, N. A. (2015, December). *Lebensqualität bei Patienten mit angeborenen Stoffwechselkrankheiten.* Workshop presentation at the Meeting of nutritionists "Update pädiatrische Diätetik", Münster, Germany.

Zeltner N. A., Landolt M. A., Baumgartner M. R., Lageder, S., Quitmann, J., Sommer, R., Mühlhausen, C., Schlune, A., Scholl-Bürgi, S., Karall, D., Huemer, M. (2015, October). *Living with intoxication-type inborn errors of metabolism - a qualitative analysis of interviews with paediatric patients and their caregivers.* Poster presentation at the Children's Research Centre Retreat, Au, Switzerland.

Zeltner N. A., Landolt M. A., Baumgartner M. R., Lageder, S., Quitmann, J., Sommer, R., Karall, D., Mühlhausen, C., Schlune, A., Scholl-Bürgi, S., Huemer, M. (2015, September). *Health-related quality of life in children and adolescents with intoxication-type inborn errors of metabolism*. Poster presentation at the Society of the Study of Inborn Errors of Metabolism (SSIEM) Symposium, Lyon, France.

Huemer, M., Zeltner, N. A., Bosch, A. (2015, June). *Quality of life in patients with inborn errors of metabolism.* Workshop presentation at the European Metabolic Group Meeting, Venice, Italy.

Zeltner, N. A., Landolt, M.A., Baumgartner, M.R., Huemer, M. (2014, December). *Lebensqualität bei Stoffwechselkrankheiten vom Vergiftungstyp.* Oral presentation at the radiz Symposium, Zürich, Switzerland.

Zeltner, N. A., Landolt, M. A., Baumgartner, M. R., Huemer, M. (2014, September). *Health-related quality of life in children and adolescents with intoxication-type inborn errors of metabolism – patients' and parents' perspectives.* Oral presentation at the Society of the Study of Inborn Errors of Metabolism (SSIEM) Symposium, Innsbruck, Austria.

Zeltner, N. A., Huemer, M., Baumgartner, M. R., Landolt M. A. (2014, May). *Health-related quality of life in children and adolescents with inborn errors of metabolism – patients' and caregivers' perspectives.* Oral presentation at the European Metabolic Group Conference, Zürich, Switzerland.

Zeltner, N. A., Huemer, M., Baumgartner, M. R., Landolt M. A. (2014, January). *Quality of life of patients with intoxication-type inborn errors of metabolism – a neglected field of research?* Oral presentation at the Austrian-Swiss Metabolic Meeting, Zürich, Switzerland.

Zeltner, N. A., Huemer, M., Baumgartner, M. R., Landolt M. A. (2013, September). *Health-related Quality of Life and Psychological Adjustment in Patients with Intoxication-type Inborn Errors of Metabolism: Preliminary Results of a Systematic Review.* Poster presentation at the 12th International Congress of Inborn Errors of Metabolism, Barcelona, Spain.

Zeltner, N. A., Baumgartner, M. R., Huemer, M., Landolt M. A. (2013, July). *Measuring Health-related Quality of Life in Children with Intoxication-type Inborn Errors of Metabolism.* Poster presentation at the 1st Rare Disease Summer School, Zürich, Switzerland.